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(54) Title: ORGANIC LIGHT EMITTING DEVICES HAVING CARRIER TRANSPORTING LAYERS COMPRISING METAL COMPLEXES

(57) Abstract: Light emitting devices having charge transporting layers comprising one or more metal complexes are provided. More particularly, devices include hole transporting layers comprising at least one metal complex are disclosed. The present devices can further comprise an electron blocking layer for improved efficiency.

ORGANIC LIGHT EMITTING DEVICES HAVING CARRIER TRANSPORTING LAYERS COMPRISING METAL COMPLEXES

CROSS REFERENCE TO RELATED APPLICATIONS

5   This application claims the benefit of Provisional Application No. 60/315,527, filed August 29, 2001, and Application No. 60/317,541, filed September 5, 2001. This application is related to copending Provisional Application No. 60/317,540, filed on the same date, which is incorporated herein by reference in its entirety.

10   ## GOVERNMENT RIGHTS

The U.S. Government has a paid-up license in this invention and the right in limited circumstances to require the patent owner to license others on reasonable terms as provided for by the terms of Contract No._____awarded by DARPA.

15   ## FIELD OF THE INVENTION

The present invention is directed to light emitting devices incorporating metal complexes for improved efficiency and stability.

BACKGROUND OF THE INVENTION

20   Electronic display currently is a primary means for rapid delivery of information. Television sets, computer monitors, instrument display panels, calculators, printers, wireless

phones, handheld computers, etc. aptly illustrate the speed, versatility, and interactivity that is characteristic of this medium. Of the known electronic display technologies, organic light emitting devices (OLEDs) are of considerable interest for their potential role in the development of full color, flat-panel display systems that may render obsolete the bulky cathode ray tubes still currently used in many television sets and computer monitors.

5   Generally, OLEDs are comprised of several organic layers in which at least one of the layers can be made to electroluminesce by applying a voltage across the device (see, e.g., Tang, *et al.*, *Appl. Phys. Lett.* **1987**, *51*, 913 and Burroughes, *et al.*, *Nature*, **1990**, *347*, 359). When a voltage is applied across a device, the cathode effectively reduces the adjacent organic layers (i.e., injects electrons) whereas the anode effectively oxidizes the adjacent

10   organic layers (i.e., injects holes). Holes and electrons migrate across the device toward their respective oppositely charged electrodes. When a hole and electron meet on the same molecule, recombination is said to occur and an exciton is formed. Recombination of the hole and electron is preferably accompanied by radiative emission, thereby producing electroluminescence.

15   Depending on the spin states of the hole and electron, the exciton which results from hole and electron recombination can have either a triplet or singlet spin state. Luminescence from a singlet exciton results in fluorescence whereas luminescence from a triplet exciton results in phosphorescence. Statistically, for organic materials typically used in OLEDs, about one quarter of the excitons are singlets and the remaining three quarters are triplets

20   (see, e.g., Baldo, *et al.*, *Phys. Rev. B*, **1999**, *60*,14422). Until the discovery that there were certain phosphorescent materials that could be used to fabricate practical electro-phosphorescent OLEDs having a theoretical quantum efficiency of up to 100% (i.e., harvesting all of both triplets and singlets), the most efficient OLEDs were typically based on materials that fluoresced. These materials fluoresced with a maximum theoretical

25   quantum efficiency of only 25% (where quantum efficiency of an OLED refers to the efficiency with which holes and electrons recombine to produce luminescence), since the triplets to ground state transition is formally a spin forbidden process. Electro-phosphorescent OLEDs have now been show to have superior overall device efficiencies as compared with electro-fluorescent OLEDs (see, e.g., Baldo, *et al.*, *Nature*, **1998**, *395*, 151

30   and Baldo, *e.g.*, *Appl. Phys. Lett.* **1999**, *75*(3), 4).

Typically, OLEDs contain several thin organic layers between a hole injecting anode layer, comprising an oxide material such as indium-tin oxide (ITO), Zn-In-SnO$_2$, SbO$_2$, or the like, and an electron injecting cathode layer, comprising a metal layer such as Mg, Mg:Ag, or LiF:Al. An organic layer residing in proximity to the anode layer is usually referred to as the "hole transporting layer" (HTL) due to its propensity for conducting

5   positive charge (i.e., holes). Various compounds have been used as HTL materials. The most common materials consist of various triaryl amines which show high hole mobilities. Similarly, the organic layer residing in proximity to the cathode layer is referred to as the "electron transporting layer" (ETL) due to its propensity to conduct negative charge (i.e., electrons). There is somewhat more variety in the ETL materials used in OLEDs as

10   compared with for the HTL. A common ETL material is aluminum tris(8-hydroxyquinolate) (Alq$_3$). Collectively, the ETL and HTL are often referred to as carrier layers. In some cases, an additional a layer may be present for enhancing hole or electron injection from the electrodes into the HTL or ETL, respectively. These layers are often referred to as hole injecting layers (HILs) or electron injecting layer (EIL). The HIL may be comprised of a

15   small molecule such as 4,4',4"-tris(30methylphenylphenylamino)triphenylamine (MTDATA) or polymeric material such as poly(3,4-ethylenedioxythiophene) (PEDOT). The EIL may be comprised of a small molecule material such as, e.g., copper phthalocyanine (CuPc). Many OLEDs further comprise an emissive layer (EL), or alternatively termed, luminescent layer, situated between the ETL and HTL, where electroluminescence occurs. Doping of the

20   luminescent layer with various luminescent materials has allowed fabrication of OLEDs having a wide variety of colors.

In addition to the electrodes, carrier layers, and luminescent layer, OLEDs have also been constructed with one or more blocking layers to help maximize efficiency. These layers serve to block the migration of holes, electrons, and/or excitons from entering inactive

25   regions of the device. For example, a blocking layer that confines holes to the luminescent layer effectively increases the probability that holes will result in a photoemissive event. Hole blocking layers desirably have a deep (i.e., low) HOMO energy level (characteristic of materials that are difficult to oxidize) and conversely, electron blocking materials generally have a high LUMO energy level. Exciton blocking materials have also been shown to

30   increase device efficiencies. Triplet excitons, which are relatively long-lived, are capable of

migrating about 1500 to 2000 Å, which is sometimes greater than the entire width of the device. An exciton blocking layer, comprising materials that are characterized by a wide band gap, can serve to block loss of excitons to non-emissive regions of the device.

In seeking greater efficiencies, devices have been experimentally created with layers containing light emitting metal complexes. Functional OLEDs having emissive layers of

5   tris(2,2'-bipyridine)ruthenium(II) complexes or polymer derivatives thereof have been reported in Gao, *et al., J. Am. Chem. Soc.,* **2000,** *122,* 7426, Wu, *et al., J. Am. Chem. Soc.* **1999,** *121,* 4883, Lyons, *et al., J. Am. Chem. Soc.* **1998,** *120,* 12100, Elliot, *et al., J. Am. Chem. Soc.* **1998,** *120,* 6781, and Maness, *et al., J. Am. Chem. Soc.* **1997,** *119,* 3987. Iridium-based and other metal-containing emitters have been reported in, e.g., Baldo, *et al.,*

10 *Nature,* **1998,** *395,* 151; Baldo, *et al., Appl. Phys. Lett.,* **1999,** *75,* 4; Adachi, *et al., Appl. Phys. Lett.,* **2000,** *77,* 904; Adachi, *et al., Appl. Phys. Lett.,* **2001,** *78,* 1622; Adachi, *et al., Bull. Am. Phys. Soc.* **2001,** *46,* 863, Wang, *et al., Appl. Phys. Lett.,* **2001,** *79,* 449, and U.S. Pat. Nos. 6,030,715; 6,045,930; and 6,048,630. Emissive layers containing (5-hydroxy)quinoxaline metal complexes as host material has also been described in U.S. Pat.

15 No. 5,861,219. Efficient multicolor devices and displays are also described in U.S. Pat. No. 5,294, 870 and International Application Publication No. WO 98/06242.

A metal-containing blocking layer has also been reported. Specifically, (1,1'-biphenyl)-4-olato)bis(2-methyl-8-quinolinolato N1,O8)aluminum (BAlq) has been used as a blocking layer in the OLEDs reported in Watanabe, *et al.* "Optimization of driving lifetime

20 durability in organic LED devices using Ir complex," in *Organic Light Emitting Materials and Devices IV,* Kafafi, ed. Proceedings of SPIE Vol.4105, p. 175 (2001).
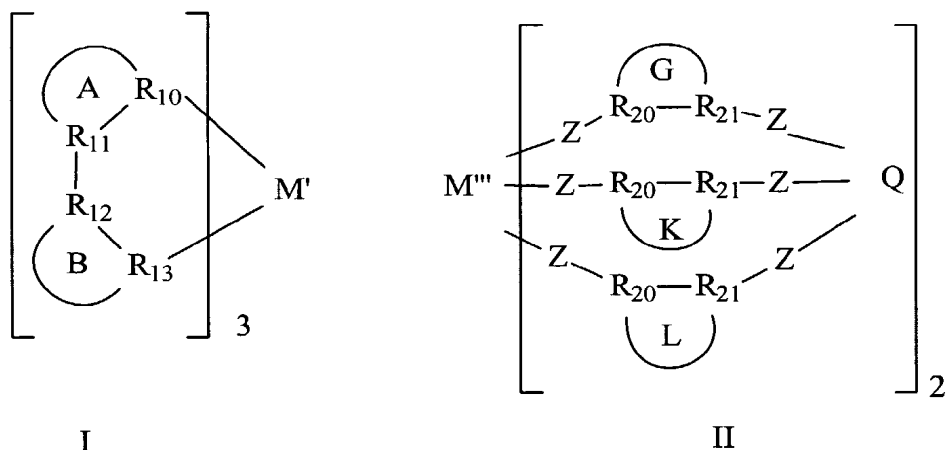
Although OLEDs promise new technologies in electronic display, they often suffer from degradation, short life spans, and loss of efficiency over time. The organic layers can be irreversibly damaged by sustained exposure to the high temperatures typically encountered

25 in devices. Multiple oxidation and reduction events can also cause damage to the organic layers. Consequently, there is a need for the development of new materials for the fabrication of OLEDs. Compounds that are stable to both oxidation and reduction, have high T_g values, and readily form glassy thin films are desirable. The invention described hereinbelow helps fulfill these and other needs.

30

SUMMARY OF THE INVENTION

The present invention provides light emitting devices comprising a hole transporting layer that includes at least one metal complex. In some embodiments, the hole transporting layer consists essentially of said metal complex or complexes. In further embodiments, the hole transporting layer comprises an organic matrix doped with said metal complex or complexes.

In some embodiments, the metal complex is coordinatively saturated, preferably wherein metal complex has a coordination number of four or six. In some embodiments, the metal the said metal complex is a transition metal, which can be a first row, second row or third row transition metal. In some embodiments, the metal of said metal complex is Fe, Co, Ru, Pd, Os or Ir, or any subcombination thereof.

In some embodiments of the light emitting devices of the invention, at least one metal complex has one of the formulas I or II:

I   II

wherein:

M′ and M‴ are each, independently, a metal atom;

R_{10}, R_{13}, R_{20} and R_{21} are each, independently, N or CH;

R_{11} and R_{12} are each, independently, N, CH, O or S;

Ring systems A, B, G, K and L are each independently a mono-, di- or tricyclic fused aliphatic or aromatic ring system optionally containing up to 5 hetero atoms;

Z is C_1-C_6 alkyl, C_2-C_8 mono- or poly alkenyl, C_2-C_8 mono- or poly alkynyl, or a bond; and

Q is BH, N, or CH.

5   In some embodiments where the metal complex has the formula I, Ring system A and Ring system B are each monocyclic. In further embodiments where the metal complex has the formula I, Ring system A is a five membered heteroaryl monocyclic ring and Ring system B is a six membered aryl or heteroaryl monocyclic ring.

In some further embodiments, R_{10} and R_{11} are N, and R_{13} is CH. In further

10   embodiments, Ring A forms pyrazole. In still further embodiments, Ring B forms phenyl.

In some embodiments of the light emitting devices of the invention, the metal of at least one of the metal complexes is a d^0, d^1, d^2,d^3,d^4,d^5, or d^6 metal. In some embodiments where the metal complex has the formula I, M' is a transition metal. In further embodiments, M' is Fe, Co, Ru, Pd, Os or Ir. In further embodiments, M' is Fe or Co. In further

15   embodiments, M' Fe, and in still further embodiments, M' is Co.

In some embodiments of the light emitting devices of the invention where the metal complex has the formula I, the metal complex is Co(ppz)$_3$.

In some embodiments of the light emitting devices of the invention, at least one metal complex has the formula II. In some embodiments of the light emitting devices of the

20   invention where at least one metal complex has the formula II, Ring systems G, K and L are each 5 or 6 member monocyclic rings. In further embodiments, the Ring systems G, K and L are each 5-membered heteroaryl monocyclic rings. In still further embodiments, R_{21} and R_{22} are each N.

In further embodiments of the light emitting devices of the invention where at least

25   one metal complex has the formula II, Ring systems G, K and L each form pyrazole. In further embodiments, M''' is a $d^{5/6}$ or $d^{2/3}$ metal.

In some embodiments of the light emitting devices of the invention where at least one metal complex has the formula II, M''' is a transition metal. In further embodiments, M''' is Fe, Co, Ru, Pd, Os or Ir. In further embodiments, M''' is Fe or Co. In further
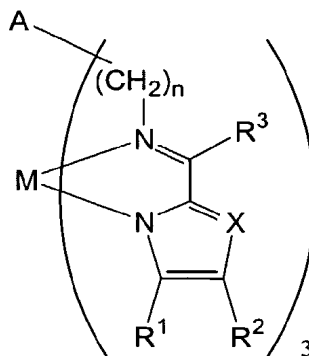
30   embodiments, M''' is Fe.

In some embodiments, the metal complex is FeTp'$_2$.

In some embodiments of the light emitting devices of the invention, the light emitting device further comprises an electron blocking layer, which can be include an organic electron blocking material, a metal complex, or both. In some embodiments, the organic electron blocking material is selected from triarylamines or benzidenes. In some embodiments, the

5   electron blocking layer consists essentially of the metal complex. In further embodiments, the electron blocking layer comprises a matrix doped with said metal complex.

In some embodiments, the electron blocking layer has a HOMO energy level close to the HOMO energy level of said hole transporting layer. In further embodiments, the electron blocking layer has a HOMO energy level higher than the HOMO energy level of

10   said hole transporting layer.

In some embodiments, the metal complex of the electron blocking layer comprises a metal selected from Ga, In, Sn, or a group 8, 9, or 10 transition metal. In some embodiments, the metal complex of said electron blocking layer comprises Ga. In further embodiments, the metal complex of the electron blocking layer comprises a multidentate

15   ligand. In some embodiments, the multidentate ligand has a bridging atom selected from N and P. In further embodiments, the multidentate ligand has a mesityl bridge moiety. In further embodiments, the multidentate ligand comprises up to three mono-, bi- or tricyclic heteroaromatic moieties.

In some embodiments, the of the light emitting devices of the invention, the electron

20   blocking layer comprises a compound having the formula III:

III

25   wherein:

M is a metal atom;

X is N or CX' where X' is H, C_1-C_{20} alkyl, C_2-C_{40} mono- or poly alkenyl, C_2-C_{40} mono- or poly alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or halo;

A is CH, CX', N, P, P(=O), aryl or heteroaryl;

each R^1 and R^2 is, independently, H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or halo; or

R^1 and R^2, together with the carbon atoms to which they are attached, link to form a fused C_3-C_8 cycloalkyl or aryl group;

R^3 is H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or halo; and

n is 1 to 5.

In some embodiments where the electron blocking layer has the formula III, M is a trivalent metal atom, X is CH or N, A is N or 1,3, 5-phenyl, each R^1 and R^2 are H, or R^1 and R^2, together with the carbon atoms to which they are attached, link to form a phenyl group, R^3 is H; and n is 1 or 2.   In further embodiments where the electron blocking layer has the formula III, M is Ga.

In further embodiments, the electron blocking layer comprises $Ga(pma)_3$.

In some embodiments of the light emitting devices of the invention, the metal complex of said hole transporting layer is $Co(ppz)_3$.   In further embodiments of the light emitting devices of the invention, the metal complex of said hole transporting layer is $FeTp'_2$.

In further embodiments of the light emitting devices of the invention, the electron blocking layer comprises $Ga(pma)_3$ and the metal complex of said hole transporting layer is $Co(ppz)_3$.

In further embodiments of the light emitting devices of the invention, the electron blocking layer comprises $Ga(pma)_3$ and the metal complex of said hole transporting layer is $FeTp'_2$.

The present invention also provides light emitting devices comprising the substructure HTL/EL or HTL/EBL/EL; wherein each of said EL, HTL, and EBL comprise at least one metal complex.

Also provided by the present invention are light emitting devices comprising the substructure HTL/EL or HTL/EBL/EL; wherein none of said EL, HTL, or EBL is comprised

solely of organic molecules.

The present invention further provides light emitting devices having a plurality of layers, the devices being devoid of a layer that is composed solely of organic molecules. In some embodiments, each of said layers contains at least one metal complex.

The present invention also provides light emitting devices comprising a hole

5   transporting layer, an emissive layer, and a blocking layer;

said hole transporting layer having a first HOMO energy, wherein said hole transporting layer comprises at least one metal complex;

said emissive layer comprising at least one material capable of transporting electrons, said material having a second HOMO energy; and

10   said blocking layer comprising a material having a HOMO energy that is between said first and second HOMO energies.

In some embodiments, the blocking layer resides between said hole transporting layer and said emissive layer. In further embodiments, the blocking layer comprises an organic electron blocking material, which can be, but is not necessarily, selected from triarylamines

15   or benzidenes. In still further embodiments, electron blocking layer comprises a metal complex.

The present invention also provides methods of facilitating hole transport in a light emitting device, said light emitting device comprising a hole transporting layer and an emissive layer;

20   said hole transporting layer comprising at least one metal complex and having a first HOMO energy;

said emissive layer comprising at least one material capable of transporting electrons, said material having a second HOMO energy higher than said HOMO energy of said hole transporting layer;

25   said method comprising the step of placing a blocking layer between said hole transporting layer and said emissive layer, wherein said blocking layer comprises a material having a HOMO energy level that is intermediate between said first and second HOMO energies.

In some embodiments of the foregoing methods, the metal complex of said hole

30   transporting layer is a complex formula I or II, as described above. In some embodiments,

the metal complex of the hole transporting layer is Co(ppz)$_3$ or FeTp'$_2$. In further embodiments, the blocking layer comprises at least one metal complex. In some embodiments, the metal complex of said blocking layer is a compound having the formula III as described above. In further embodiments, the metal complex of the blocking layer is Ga(pma)$_3$. In further embodiments, the hole transporting layer comprises Co(ppz)$_3$ or FeTp'$_2$,

5   and said barrier layer comprises Ga(pma)$_3$.

The present invention also provides methods of fabricating a light emitting device, said method comprising placing a hole transporting layer in electrical contact with an emissive layer, wherein said hole transporting layer comprises a compound of formulas I or II as described above. In some embodiments, the light emitting device further comprises an

10   electron blocking layer. In further embodiments, the electron blocking layer comprises a compound having the formula III as described above. In further embodiments, the electron blocking layer comprises Ga(pma)$_3$. In further embodiments, the compound is a compound of formula I, and is Co(ppz)$_3$ or FeTp'$_2$. In further embodiments, the compound if Co(ppz)$_3$.

The present invention also provides methods of transporting holes in a hole

15   transporting layer of a light emitting device, wherein said hole transporting layer comprises at least one metal complex, said method comprising applying a voltage across said device.

Also provided by the present invention are pixels and displays comprising the devices described herein.

20   **BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 compares plots of quantum efficiency v. current density for devices of the structure ITO/NPD(500 Å)/Alq$_3$(600 Å)/MgAg and ITO/Co(ppz)$_3$(500 Å)/Alq$_3$(600 Å)/MgAg.

Figure 2 compares plots of current density v. voltage for devices of the structure

25   ITO/NPD(500 Å)/Alq$_3$(600 Å)/MgAg and ITO/Co(ppz)$_3$(500 Å)/Alq$_3$(600 Å)/MgAg.

Figure 3 compares plots of current density v. voltage for devices of the structure ITO/NPD(500 Å)/Alq$_3$(600 Å)/MgAg and ITO/Co(ppz)$_3$(500 Å)/Alq$_3$(600 Å)/MgAg.

Figure 4A-4C compares plots of quantum efficiency v. current density for devices comprising Co(ppz)$_3$.

Figure 5 compares plots of current density v. voltage for devices comprising Co(ppz)$_3$.

Figures 6A-6B show electronic spectra for Ga(pma)$_3$.

Figure 7 shows a current density v. voltage plot for a device having the structure ITO/Co(ppz)$_3$(400Å)/Ga(pma)$_3$(100Å)/Alq$_3$(500Å)/MgAg(1000Å)/Ag.

Figure 8 shows a luminance v. voltage plot for devices of the structure ITO/Co(ppz)$_3$(400 Å)/Ga(pma)$_3$(100 Å)/Alq$_3$(500 Å)/MgAg(1000 Å)/Ag.

Figure 9 shows an external quantum efficiency v. voltage plot for devices of the structure ITO/Co(ppz)$_3$(400 Å)/Ga(pma)$_3$(100 Å)/Alq$_3$(500 Å)/MgAg(1000 Å)/Ag.

Figure 10 shows an external quantum efficiency v. current density plot for devices of the structure ITO/Co(ppz)$_3$(400 Å)/Ga(pma)$_3$(100 Å)/Alq$_3$(500 Å)/MgAg(1000 Å)/Ag.

Figures 11A-11B show current density v. voltage and brightness v. voltage plots for devices having the structure ITO/HTL(500 Å)/CBP:Irppy(6%)(200 Å)/BCP(150 Å)Alq$_3$(200 Å)/LiF/Al.

Figures 12A-12B show quantum efficiency v. current density and emission spectrum plots for devices having the structure ITO/HTL(500 Å)/CBP:Irppy(6%)(200 Å)/BCP(150 Å)Alq$_3$(200 Å)/LiF/Al.

Figure 13 shows a plot of current v. voltage for devices of the structure ITO/Co(ppz)$_3$(400 Å)/NPD(100 Å)/Alq$_3$(500 Å)/Mg:Ag(1000 Å)/Ag(400 Å).

Figure 14 shows a plot of brightness v. voltage for devices of the structure ITO/Co(ppz)$_3$(400 Å)/NPD(100 Å)/Alq$_3$(500 Å)/Mg:Ag(1000 Å)/Ag(400 Å).

Figures 15A-15B show a plots of quantum efficiency v. voltage and quantum efficiency v. current density for devices of the structure ITO/Co(ppz)$_3$(400 Å)/NPD(100 Å)/Alq$_3$(500 Å)/Mg:Ag(1000 Å)/Ag(400 Å).

Figure 16 illustrates some hole transporting materials.

Figure 17 illustrates some metal complexes suitable in layers of the devices of the present invention.

Figure 18 describes aspects of carrier migration

Figure 19 shows chemical syntheses of metal complexes suitable in devices of the present invention.

Figure 20 shows absorption spectra of several Co compounds suitable in devices of the present invention.

Figure 21 shows cyclic voltammograms for Co complexes suitable in devices of the present invention.

Figure 22 illustrates properties of devices comprising Co compounds.

Figure 23 illustrates properties of devices comprising $Co(ppz)_3$ and an NPD electron blocking layer.

Figure 24 illustrates photophysical properties of $Ga(pma)_3$.

Figure 25 illustrates properties of devices devoid of a purely organic layer.

Figure 26 illustrates properties of devices devoid of a purely organic layer.

Figure 27 compares properties of devices comprising NPD with properties of devices comprising Co and Ga metal complexes instead of NPD.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

As used herein, the terms "low" and "deep," in reference to molecular orbital energies, are used interchangeably. Lower and deeper generally describe molecular orbitals residing at a lower, or more stable, energy level. Ionization of electrons from deeper orbitals requires more energy than ionization of electrons in shallower, or higher, orbitals. Thus, although the deeper orbitals are said to be lower, they are often referred to numerically by higher numbers. For example, a molecular orbital residing at 5.5 eV is lower (deeper) than a molecular orbital residing at 2.5 eV. Similarly, the terms "shallow" and "high" in reference to orbital energy levels, refer to orbitals at less stable energies. These terms are well known to those skilled in the art.

As used herein, the term "adjacent," in reference to layers of light emitting devices, refers to layers having contacting sides. For example, a first layer and a second layer that are adjacent to one another describe, for example, contacting layers where one side of one layer is in contact with one side of the other layer.

As used herein, the term "gap" or "band-gap" generally refers to an energy difference, such as, for example, between a HOMO and a LUMO. A "wider gap" refers to an energy difference that is greater than for a "narrower gap" or "smaller gap." A "carrier gap" refers to the energy difference between the HOMO and LUMO of a carrier.

The present invention is directed to, *inter alia*, light emitting devices comprising one or more layers that in turn comprise at least one metal complex. Devices, as such, may have higher efficiencies and higher stability as compared with devices having traditional organic blocking layers.

The light emitting devices of the present invention are typically layered structures that

5   electroluminesce when a voltage is applied across the device. Typical devices are structured so that one or more layers are sandwiched between a hole injecting anode layer and an electron injecting cathode layer. The sandwiched layers have two sides, one facing the anode and the other facing the cathode. These sides are referred to as the anode side and the cathode side, respectively. Layers are generally deposited on a substrate, such as glass, on

10   which either the anode layer or the cathode layer may reside. In some embodiments, the anode layer is in contact with the substrate. In many cases, for example when the substrate comprises a conductive or semi-conductive material, an insulating material can be inserted between the electrode layer and the substrate. Typical substrate materials, that may be rigid, flexible, transparent, or opaque, include glass, polymers, quartz, sapphire, and the like.

15   Hole transporting layers are placed adjacent to the anode layer to facilitate the transport of electrons. In some embodiments, a hole injecting layer for enhancing hole injection, sometimes referred to as a hole injecting enhancement layer, may be placed adjacent to the anode, between the anode and the HTL. Materials suitable for the HTL include any material that is known by one skilled in the art to function as such. Suitable

20   materials are typically easy to oxidize and include triaryl amines such as N,N'-diphenyl-N,N'-bis(3-methylphenyl)1-1'biphenyl-4,4'diamine (TPD), 4,4'-bis[N-(1-naphthyl)-N-phenyl-amino]biphenyl (α-NPD), 4,4'-bis[N-(2-naphthyl)-N-phenyl-amino]biphenyl (β-NPD), and the like. Metal complexes may also be used in HTLs. Some suitable metal complexes are described, for example, in Application Ser. No. 60/283,814, filed April 13, 2001, which is

25   incorporated herein by reference in its entirety. Similarly, ETLs are situated adjacent to the cathode layer to facilitate transport of electrons. An electron injecting enhancement layer can optionally be placed adjacent to ETL or cathode layer. Materials suitable for the ETL include any materials known in the art to function as such. Typical ETL materials are relatively easy to reduce and can include, for example, aluminum tris(8-hydroxyquinolate) (Alq_3),

30   carbazoles, oxadiazoles, triazoles, thiophene, oligothiophene, and the like. HTL and ETL

carrier layers can have thicknesses ranging from about 100 to about 1000 Å. Since it is typically the site of exciton formation and luminescence, the EL layer is preferably somewhere between the HTL and ETL. The EL can optionally be in contact with one or both of the HTL and ETL or may be flanked by one or more blocking layers. EL materials can include, for example dye-doped Alq_3 and the like. In some embodiments, neat (un-doped)

5   films of luminescent material may be used as the emissive layer. Furthermore, layers can serve dual functions. For example, an ETL or HTL can also function as an EL.

In some embodiments according to the present invention, devices comprise at least one charge transport layer (i.e., carrier layer), such as, for example, a HTL, ETL, hole injecting layer, or electron injecting layer, that comprises at least one metal complex. The

10   carrier layer can be a thin film consisting essentially of metal complex or an organic matrix doped with metal complex. In some preferred embodiments, devices of the present invention comprise a hole blocking layer that includes at least one metal complex. Accordingly, in some embodiments, the metal complexes of the HTLs can be selected such that their HOMO energy levels will support hole transport. Thus, in some embodiments, it is preferable to

15   select metal complexes having HOMO energy levels in the range of from about 7 to 4.5 eV and LUMO energy levels in the range of from about 2 to about 4 eV.

Metal complexes that are suitable for use in devices as a charge transport layer can be selected on the basis of properties that facilitate this function. For example, a hole transporting material typically undergoes one electron oxidation. Thus, metal complexes that

20   are stable to one electron oxidation processes can be suitable as hole transporters. Similarly, metal complexes that are stable to one electron reductions can be suitable as a electron transporting materials. Stable oxidation and reduction processes can be identified by electrochemical methods such as cyclic voltammetry, which is further discussed below. Another consideration is charge mobility. For example, materials having high hole

25   mobilities can generally function as good hole transporters. Charge mobility often corresponds with low reorganizational energies for redox processes. Thus, for example, metal complexes showing little structural differences when oxidized or reduced typically have a relatively small energy barrier (reorganizational energy) associated with oxidation or reduction. Certain metal properties such as electron configuration can affect reorganizational

30   barriers, as is well known in the art and further discussed below. Additionally, certain ligand

properties, such as denticity, can affect reorganizational barriers of redox events in metal complexes, the details of which are also further discussed below.

In some embodiments, it is desirable that one or more layers of the device comprise one or more dopants. Emissive dopants (i.e., photoemitting molecules, emitters) can be included in at least one layer, such as for example the EL, for improved efficiency and color
5   tunability. Doped layers usually comprise a majority of host material and minority of dopant. Host material (also referred to as matrix) typically transfers excitons through a non-radiative process to the emissive dopant material, which then emits light of a wavelength characteristic of the dopant, rather than the host.

Dopants can also serve to trap charge. For example, the LUMO levels of the host and
10   dopant can be arranged such that the LUMO level of the dopant is lower than the LUMO level of the host, such that the dopant molecule can act as an electron trap. Similarly, the HOMO levels of the host and dopant can be arranged such that the HOMO level of the dopant is higher than the HOMO level of the host, such that the dopant molecule would act as a hole trap. In addition, one or more dopants, referred to as transfer dopants, can be used
15   to facilitate the transfer of energy from the host to the emissive dopant. For example, cascade doping can be used, which involves the non-radiative transfer of excitons from a molecule of the host through one or more transfer dopants to the emissive dopant. These intermediate transfers can be by Förster transfer, Dexter transfer, hole trapping or electron trapping that eventually leads to the formation of an exciton on the transfer dopant or the emissive dopant,
20   or by any other suitable mechanism.

Dopants can be present in the host material in quantities ranging, for example, from about 0.1% to about 50%, from about 1% to about 20%, or from 1% to about 10% by weight. A level of about 1% by weight of doping is preferred for emissive dopants in host material. Alternatively, in some embodiments, levels of dopant result in an average intermolecular
25   distance between dopant molecules of about the Förster radius of the dopant, such as, for example, from about 20 to about 40 Å, or from about 25 to about 35 Å, or about 30 Å. Emissive dopants can include any compound that is capable of photoemission. Emissive dopants include fluorescent organic dyes, such as laser dyes, as known and used in the art. Preferred emissive dopants include phosphorescent metal complexes such as the Ir, Pt, and
30   other heavy metal complexes disclosed in Application Ser. Nos. 08/980,986, filed December

1, 1997, 09/883,734, filed June 18, 2001, and 60/283,814, filed April 13, 2001, each of which is herein incorporated by reference in its entirety.

In some embodiments, devices of the present invention comprise at least one blocking layer. Blocking layers (BLs) function to confine holes, electrons, and/or excitons to specific regions of the light emitting devices. For example, device efficiency can be increased when excitons are confined to the EL and/or when holes and electrons are prevented from migrating out of the EL. Blocking layers can serve one or more blocking functions. For example, a hole blocking layer can also serve as an exciton blocking layer. In some embodiments, the hole blocking layer does not simultaneously serve as an emissive layer in devices of the present invention. Although a blocking layer can include compounds that are capable of emitting, emission can occur in a separate emissive layer. Thus, in preferred embodiments, the blocking layer does not luminesce. Blocking layers can be thinner than carrier layers. Typical blocking layers have thicknesses ranging from about 50 Å to about 1000 Å, or from about 50 Å to about 750 Å, or from about 50 Å to about 500 Å. Additionally, blocking layers preferably comprise compounds other than BAlq.

Hole blocking layers (HBLs) are typically comprised of materials that have difficulty acquiring a hole. For example, hole blocking materials can be relatively difficult to oxidize. In most instances, hole blocking materials are more difficult to oxidize than an adjacent layer from transporting holes. A material that is more difficult to oxidize than another material typically possesses a lower HOMO energy level. For example, holes originating from the anode and migrating into an EL can be effectively blocked from exiting the EL (on the cathode side) by placing a blocking layer of material adjacent to the EL on the cathode side of the device. The blocking layer preferably has a HOMO energy level lower than the HOMO energy levels of the EL. Larger differences in HOMO energy levels correspond to better hole blocking ability. The HOMO of the materials of the blocking layer are preferably at least about 50, 100, 200, 300, 400, 500 meV (milli-electronvolts) or more deeper than the HOMO level of an adjacent layer in which holes are to be confined. In some embodiments, the HOMO of the materials of the blocking layer are at least about 200 meV deeper than the HOMO level of an adjacent layer in which holes are to be confined.

In some devices of the invention, the layer in which holes are to be confined can comprise more than one material, such as a host material (matrix) and a dopant. In this case,

a HBL preferably has a HOMO energy level that is lower (deeper) than the material of the adjacent layer which carries the majority of positive charge (i.e., the material with the highest (shallowest) HOMO energy level). For example, an emissive layer can comprise a host material having a deeper HOMO energy level than the dopant. In this case, the dopant acts as a trap for holes and can be the principle hole transporter of the emissive layer. Thus, in such embodiments, the HOMO energy of the dopant is considered when selecting a hole blocking layer. Thus, in some embodiments, the HOMO energy level of the HBL can be higher than the host material and lower than that of the dopant.

Hole blocking layers are also preferably good electron injectors. Accordingly, the LUMO energy level of the HBL is preferably close to the LUMO energy level of the layer in which holes are to be confined. Differences in LUMO energy levels between the two layers in some embodiments can be less than about 500 meV, 200 meV, 100 meV, 50 meV, or even smaller. Hole blocking layers that are also good electron injectors typically have smaller energy barriers to electron injection than for hole leakage. Accordingly, the difference between the LUMO energies of the HBL and the layer in which holes are to be confined (corresponding to an electron injection energy barrier) is smaller than the difference in their HOMO energies (i.e., hole blocking energy barrier).

Conversely, electron blocking layers (EBLs) are comprised of materials that have difficulty acquiring electrons (i.e., are relatively difficult to reduce). In the context of a light emitting device, EBLs are preferably more difficult to reduce than the adjacent layer from which electrons migrate. A material that is more difficult to reduce than another material generally has a higher LUMO energy level. As an example, electrons originating from the cathode and migrating into an EL layer can be blocked from exiting the EL (on the anode side) by placing a blocking layer adjacent to the anode side of the EL where the blocking layer has a LUMO energy level higher than the LUMO energy level of the EL. Larger differences in LUMO energy levels correspond to better electron blocking ability. The LUMO of the materials of the blocking layer are preferably at least about 50 meV, 100 meV, 200 meV, 300 meV, 400 meV, 500 meV or more higher (shallower) than the LUMO level of an adjacent layer in which holes are to be confined. In some embodiments, the LUMO of the materials of the blocking layer can be at least about 200 meV higher (shallower) than the LUMO level of an adjacent layer in which holes are to be confined.

In some embodiments, the layer in which electrons are to be confined can comprise more than one material, such as a host material (matrix) and a dopant. In this case, an EBL preferably has a LUMO energy level that is higher than the material of the adjacent layer which carries the majority of negative charge (e.g., either the host or dopant having the lowest LUMO energy level). For example, an emissive layer can include a host material

5   having a deeper LUMO energy level than the dopant. In this case, the host can be the principle electron transporter of the emissive layer. In such embodiments, the LUMO energy level of the EBL can be higher than the host material and lower than that of the dopant. Similarly, if the dopant served as the primary carrier of electrons, then the EBL preferably has a higher LUMO than the dopant.

10   Electron blocking layers are also preferably good hole injectors. Accordingly, the HOMO energy level of the EBL is preferably close to the HOMO energy level of the layer in which electrons are to be confined. Differences in HOMO energy levels between the two layers in some embodiments can be less than about 500 meV, 200 meV, 100 meV, 50 meV, or even smaller. Electron blocking layers that are also good hole injectors typically have

15   smaller energy barriers to hole injection than for electron leakage. Accordingly, the difference between the HOMO energies of the EBL and the layer in which electrons are to be confined (corresponding to an hole injection energy barrier) is smaller than the difference in their LUMO energies (i.e., electron blocking energy barrier).

Migration of excitons from the EL to other parts of the devices can be blocked with

20   materials that have difficulty acquiring excitons. Transfer of an exciton from one material to another may be prevented when the receiving material has a wider (greater) optical gap than the exciton donating material. For example, excitons can be substantially confined to the EL layer of a device by placing, adjacent to the EL layer, an exciton blocking layer having a wider optical gap than the materials comprising the EL layer. Exciton blocking

25   layers can also be placed on either side of the EL. Exciton blocking layers can also serve as HBLs or EBLs, depending on the energy levels of the HOMO or LUMO of the exciton blocking material compared with those of adjacent layers (as discussed above). Additionally, exciton blocking layers can be good electron or hole injectors when either the HOMO or LUMO energy level of the exciton blocking layer is close in energy to the

30   respective HOMO or LUMO energy level of an adjacent layer. For example, in devices

having an exciton blocking layer and an emissive layer, the exciton blocking layer can have a HOMO energy level that is less than about 500, 200, or 100 meV from the HOMO energy level of said emissive layer. Conversely, the exciton blocking layer can have a LUMO energy level that is less than about 500, 200, 100 meV from the LUMO energy level of said emissive layer.

5   According to some embodiments of the present invention, blocking layers can also comprise dopants. As an example, the blocking layer can be comprised of a wide band-gap matrix (host) material doped with a smaller band-gap dopant. Depending on the matrix and dopant combination, the effective LUMO energy of the blocking layer can be lowered by the presence of dopant, consequently improving the electron conduction and injection properties

10   of a hole blocking layer. Conversely, the effective HOMO energy of the blocking layer can be raised by the presence of dopant, thereby improving hole injection properties. As an example, in some embodiments, HBLs comprise a wide band-gap matrix doped with a smaller band-gap material where the deep HOMO energy level of the matrix serves to prevent transport of holes and the relatively shallow LUMO level of the dopant favors

15   electron injection. In some embodiments of the invention, the matrix can comprise a substantially conjugated organic molecule such as, for example, octaphenyl cyclooctatetraene (OPCOT), oligophenylenes such as hexaphenyl, and other similar materials having a wide band-gap. Suitable matrix band gap values can be at least about 3 eV, but can also be at least about 2.5 eV, 3.0 eV, 3.3 eV, 3.5 eV or higher. Dopant is preferably a metal complex.

20   Doping levels can range from about 1% to about 50%, or more preferably from about 5% to about 20%, or even more preferably from about 10 to about 15% by weight. An example of a suitable metal complex used as a dopant for blocking layers is bis(2-(4,6-difluorophenyl)pyridyl-N, C2')iridium(III) picolinate (FIrpic). An example of hole blocking layer comprising a matrix doped with a metal complex is OPCOT doped with 15% by weight

25   of FIrpic (OPCOT:FIrpic(15%)). For example, OPCOT:FIrpic can effectively confine holes to an emissive layer comprising CBP doped with $Ir(ppy)_3$ (tris(2-phenylpyridyl-N, C2')iridium(III), Irppy) because the HOMO of OPCOT is lower than the HOMO of Irppy and the LUMO of FIrpic is higher than the LUMO of CBP.

            Metal complexes used in the devices of the present invention include any metal

30   coordination complex comprising at least one metal atom and at least one ligand. Metal

complexes can be charged or uncharged; however, uncharged complexes are more amenable to the thin layer deposition techniques used in OLED fabrication. Metal complexes are preferably stable to both one electron oxidation and one electron reduction processes. Redox-stable complexes can be identified, for example, by cyclic voltammetry (e.g., identification of reversible redox events). Additionally, such metal complexes often have low reorganizational energy barriers associated with oxidation and reduction. Accordingly, complexes having low reorganizational energy barriers show little structural difference between resting state, oxidized, and reduced state. Metal complexes typically characterized as having low reorganizational energy barriers include complexes having d^0, d^1, d^2, d^3, d^4, d^5 and d^6 electron configurations. For example, octahedral complexes having d^3 or d^6 metals typically generally have low reorganizational energy barriers. Metal complexes in which redox events affect predominantly non-bonding molecular orbitals (such as the t_{2g} set in octahedral transition metal complexes) generally have low reorganizational energy barriers, since little structural change is seen in the ligand set upon oxidation or reduction. Reorganizational energy associated with redox events can also be modulated by the ligand set. For example, multidentate ligands can structurally impose a certain coordination geometry in metal complexes. Relatively rigid tridentate, tetradentate, hexadentate ligands, and the like can constrain coordination geometry such that redox events do not result in significant structural reorganization. Additionally, metal complexes that are coordinatively saturated, such as six-coordinate complexes, which are less likely to have significant structural change associated with oxidation or reduction, are also preferred. Four-coordinate complexes can also be suitable and can include both tetrahedral and square-planar complexes as well as others. Octahedral complexes are also suitable due to their propensity for forming glassy films. Metal complexes comprising aromatic ligands may help facilitate redox processes, preferably in those instances where redox events are largely centered on the ligand. Furthermore, metal complexes comprising heavy metals are preferred over those with lighter metals for their greater thermal stability. For example, complexes comprising second and third row transition metals are preferred.

Any metal atom, in any of its accessible oxidation states, is suitable in metal complexes, including main group, transition metals, lanthanides, actinides, alkaline earth, and alkali metals. Transition metals include Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, Y, Zr, Nb,

Mo, Tc, Ru, Rh, Pd, Ag, Cd, Hf, Ta, W, Re, Os, Ir, Pt, Au, and Hg. Main group metals include Al, Ga, Ge, In, Sn, Sb, Tl, Pb, Bi, and Po. In some embodiments, metals having an atomic number greater than about 13, 36, or 54 are preferred.

Metal complexes can include any suitable ligand system. Suitable ligands can be monodentate, bidentate, multidentate, π-bonding, organic, inorganic, charged, or uncharged.
5 Further, ligands preferably comprise one or more heteroatoms through which the metal atom is coordinated, although organometallic compounds comprising coordinating carbon are also suitable and also considered as metal complexes. Coordinating heteroatoms of the ligands can include oxygen, nitrogen, sulphur, phosphorus, and the like. Nitrogen-containing ligands can include amines, nitrenes, azide, diazenes, triazenes, nitric oxide, polypyrazolylborates,
10 heterocycles such as 2,2'-bipyridine (bpy), 1,10-phenanthroline, terpyridine (trpy), pyridazine, pyrimidine, purine, pyrazine, pyridine, 1,8-napthyridine, pyrazolate, imidazolate, and macrocycles including those with and without a conjugated π system, and the like. Phosphorus-containing ligands typically include phosphines and the like. Oxygen-containing ligands include water, hydroxide, oxo, superoxide, peroxide, alkoxides, alcohols, aryloxides,
15 ethers, ketones, esters, carboxylates, crown ethers, β-diketones, carbamate, dimethylsulfoxide, and oxo anions such as carbonate, nitrate, nitrite, sulfate, sulfite, phosphate, perchlorate, molybdate, tungstate, oxalate and related groups. Sulfur-containing ligands can include hydrogen sulfide, thiols, thiolates, sulfides, disulfides, thioether, sulfur oxides, dithiocarbamates, 1,2-dithiolenes, and the like. Ligands comprising coordinating
20 carbon atoms can include cyanide, carbon disulfide, alkyl, alkenes, alkynes, carbide, cyclopentadienide, and the like. Halides can also serve as ligands. Metal complexes containing these and other ligands are described in detail in Cotton and Wilkinson, *Advanced Inorganic Chemistry*, Fourth Ed., John Wiley & Sons, New York, 1980, which is incorporated herein by reference in its entirety. Additional suitable ligands are described in
25 Application Ser. Nos. 60/283,814, filed April 13, 2001 and 09/883,734, filed June 18, 2001, each of which is incorporated herein by reference in its entirety.

Ligands, especially neutral ligands, can be further derivatized with one or more substituents, including anionic groups, to fully or partially neutralize any positive formal charge associated with the metal atoms of the metal complexes. Suitable anionic
30 substitutents can include carbonate, nitrate, nitrite, sulfate, sulfite, phosphate, and the like.

Examples of suitable metal complexes for use in hole transporting layers can include, *inter alia,* transition metal complexes having first, second, or third row transition metals, including, for example, Fe,Co, Ru, Pd, Os, and Ir. Further examples include coordinatively saturated complexes and complexes that are six- or four-coordinate.

In some embodiments of the present invention, devices comprise a hole blocking layer comprising at least one metal complex of Formula I or II:
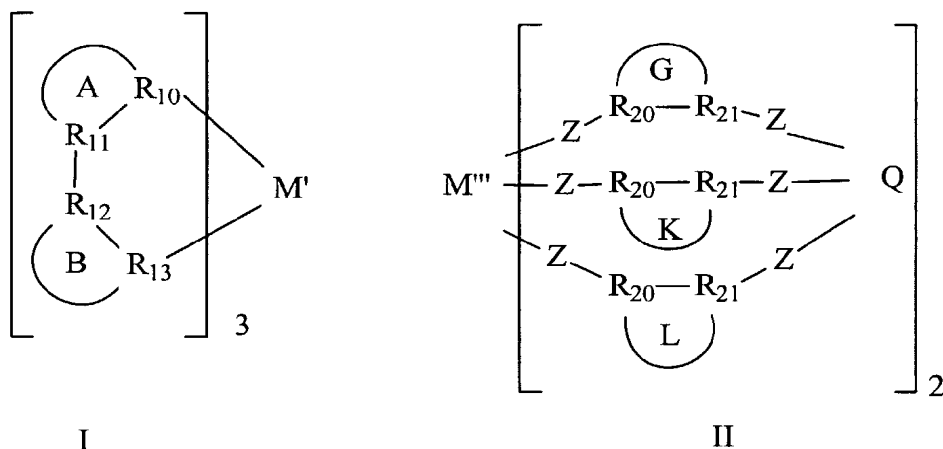
I   II

wherein:

M′ and M‴ are each, independently, a metal atom;

R_{10}, R_{13}, R_{20} and R_{21} are each, independently, N or CH;

R_{11} and R_{12} are each, independently, N, CH, O or S;

Ring systems A, B, G, K and L are each independently a mono-, di- or tricyclic fused aliphatic or aromatic ring system optionally containing up to 5 hetero atoms;

Z is C_1-C_6 alkyl, C_2-C_8 mono- or poly alkenyl, C_2-C_8 mono- or poly alkynyl, or a bond; and

Q is BH, N, or CH.

A particularly suitable compound of the above Formula I is Co(ppz)$_3$, the structure of which is shown below.
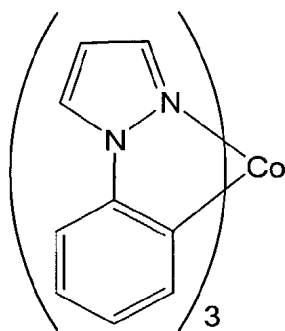
Co(ppz)₃

Another particularly suitable compound of the above Formula II is iron

trispyrazolylborate (FeTp'$_2$), the structure of which is shown below.
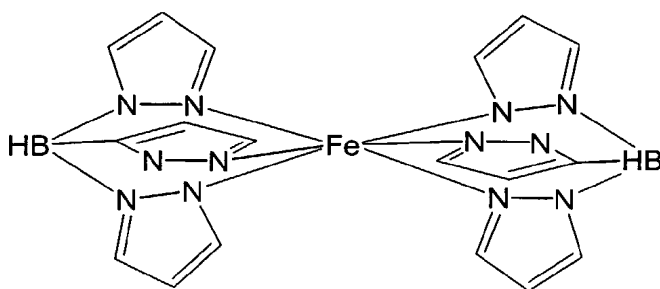
FeTp'$_2$

Metal complexes suitable for hole blocking layers can include, *inter alia*, complexes

of Os, Ir, Pt, and Au, including those described in Application Ser. Nos. 08/980,986, filed

December 1, 1997, 09/883,734, filed June 18, 2001, and 60/283,814, filed April 13, 2001,

each of which is herein incorporated by reference in its entirety. An example of a metal

complex suitable in hole blocking layers is bis(2-(4,6-difluorophenyl)pyridyl-N,

C2')iridium(III) picolinate (FIrpic), the structure of which is shown below.
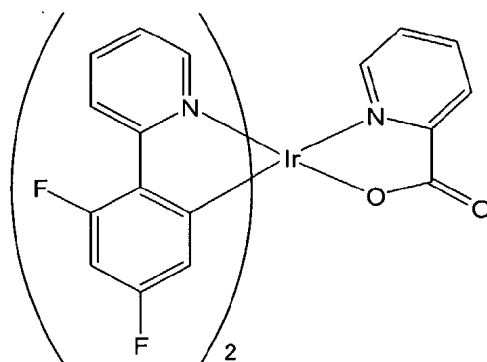
bis(2-(4,6-difluorophenyl)pyridyl-N, C2')iridium(III) picolinate (FIrpic)

Metal complexes suitable for electron blocking layers include those that are relatively difficult to reduce (i.e., high LUMO energy level). Suitable metal complexes include metal

5   complexes of the formula:
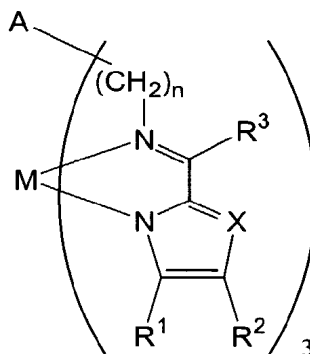
M is a metal atom;

X is N or CX' where X' is H, C_1-C_{20} alkyl, C_2-C_{40} mono- or poly alkenyl, C_2-C_{40}

10   mono- or poly alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or halo;

A is CH, CX', N, P, P(=O), aryl or heteroaryl;

each R^1 and R^2 is, independently, H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl,

C_3-C_8 cycloalkyl, aryl, aralkyl, or halo; or

R^1 and R^2, together with the carbon atoms to which they are attached, link to form

15   a fused C_3-C_8 cycloalkyl or aryl group;

R^3 is H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl, C_3-C_8 cycloalkyl, aryl,

aralkyl, or halo; and

n is 1 to 5.

In some preferred embodiments, M is a trivalent metal such as Al or Ga. Variable A

20   may preferably be CR^3 or N. R^1 and R^2, in some embodiments, join to form a fused aromatic

ring such as phenyl or pyridyl. A particularly suitable compound of the above formula is

gallium(III)tris[2-(((pyrrole-2-yl)methylidene)amino)ethyl]amine (Ga(pma)$_3$) shown below.

Ga(pma)₃
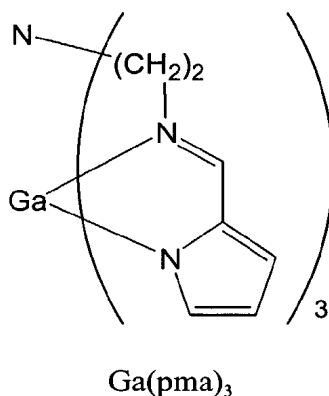
Other suitable metal complexes may have the formula
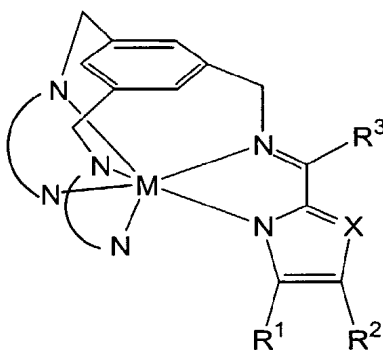
wherein:

M is a metal atom;

is N or CX' where X' is H, C_1-C_{20} alkyl, C_2-C_{40} mono- or poly alkenyl, C_2-C_{40} mono- or poly alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or halo;

each R^1 and R^2 is, independently, H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or halo; or

R^1 and R^2, together with the carbon atoms to which they are attached, link to form a fused C_3-C_8 cycloalkyl or aryl group; and

R^3 is H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or halo.

As referred to throughout the present disclosure, alkyl groups include optionally substituted linear and branched aliphatic groups. Cycloalkyl refers to cyclic alkyl groups, including, for example, cyclohexyl and cyclopentyl, as well as heterocycloalkyl groups such as pyranyl, and furanyl groups. Cycloalkyl groups may be optionally substituted. Alkenyl groups may be substituted or unsubstituted and comprise at least one carbon-carbon double

bond. Alkynyl groups may be substituted or unsubstituted and comprise at least one carbon-carbon triple bond. Aryl groups are aromatic and substituted aromatic groups having about 3 to about 50 carbon atoms, including, for example, phenyl and naphthyl. Heteroaryl groups are aromatic or substituted aromatic groups having from about 3 to about 50 carbon atoms and comprising at least one heteroatom. Examples of heteroaryl groups include pyridyl and imidazolyl groups. Aralkyl groups can be substituted or unsubstituted and have about 3 to about 30 carbon atoms, and include, for example, benzyl. Heteroaralkyl include aralkyl groups comprising at least one hetero atom. Halo includes fluoro, chloro, bromo, and iodo. Substituted groups may contain one or more substituents. Suitable substituents may include, for example, H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 heterocycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, halo, amino, azido, nitro, carboxyl, cyano, aldehyde, alkylcarbonyl, aminocarbonyl, hydroxyl, alkoxy, and the like. Substituents can also be electron-withdrawing groups and electron-donating groups. As used herein, the term "hetero" is intended to denote a non-carbon atom, for example N, O, or S.

Metal complexes suitable for exciton blocking layers include those that have relatively wide optical gaps. Metal complexes suitable for the preparation of hole blocking layers include high energy absorbers and emitters, such as for example, blue emitters. Preferred metal complexes include those in which the metal has a closed valence shell (no unpaired electrons). As a result, many preferred metal complexes for preparing exciton blocking layers are colorless, since their optical gap energy falls outside the visible range. Further, complexes having heavy metals are preferred. For example, heavy metals of the second and third row transition series tend to have larger optical gaps due to a stronger ligand field. Examples of suitable metal complexes for exciton blocking layers include, *inter alia*, complexes of Os, Ir, Pt, and Au, such as those described in Application Ser. Nos. 08/980,986, filed December 1, 1997, 09/883,734, filed June 18, 2001, and 60/283,814, filed April 13, 2001, each of which is herein incorporated by reference in its entirety. In some embodiments, metal complexes suitable for exciton blocking layers include FIrpic, Ga(pma)$_3$, and related compounds.

According to some embodiments of the present invention, devices can include a hole transporting layer that includes at least one metal complex, and, in some embodiments, an electron blocking layer that includes, for example, organic material, a metal complex, or

both. Suitable organic materials include any organic electron blocking material known in the art such as, for example, triarylamines or benzidenes. In some embodiments, the electron blocking layer resides between the HTL and EL. Accordingly, the electron blocking layer can be selected such that the HOMO energy level of the electron blocking layer falls between the HOMO energy levels of the HTL and EL. In other embodiments, the HOMO energy

5   level of the electron blocking layer is close to the HOMO energy level of the hole transporting layer. For example, the magnitude of the difference between the HOMO energy levels of the electron blocking layer and the hole transporting layer can be about 500, 200, 100, 50 meV or less. Examples of metal complexes suitable as electron blocking layers include complexes having Ga, In, Sn or a transition metal such as a group 8, 9, or 10

10   transition metal. Other examples of suitable metal complexes include complexes having multidentate ligands. A particularly suitable metal complex is Ga(pma)$_3$.

While the metal complexes of the metal complex-containing HTLs described herein can impart charge-carrying and/or blocking functions, the metal complexes also provide the additional advantage of increasing the thermal stability of devices of the invention. This is

15   significant because OLEDs and similar light emitting devices can be subject to elevated temperatures for prolonged periods of time, and such exposure is thought to be a limiting factor in the lifetimes of such devices. Accordingly, devices of the invention containing for example, complexes of heavy metals such as second and third row transition metals and fourth and fifth row main group metals are envisaged to benefits in terms of lifetime of the

20   device.

The HOMO and LUMO energy levels for OLED materials, can be measured, or estimated, in several ways known in the art. The two common methods for estimating HOMO energy levels include solution electrochemistry, such as cyclic voltammetry, and ultraviolet photoelectron spectroscopy (UPS). Two methods for estimating LUMO levels

25   include solution electrochemistry and inverse photoemission spectroscopy. As discussed above, alignment of the HOMO and LUMO energy levels of adjacent layers can control the passage of holes and electrons between the two layers.

Cyclic voltammety is one of the most common methods for determining oxidation and reduction potentials of compounds. This technique is well known to those skilled in the

30   art, and a simple description of this process follows. A test compound is dissolved along

with a high concentration of electrolyte. Electrodes are inserted and the voltage scanned in either the positive or negative direction (depending on whether an oxidation or reduction is being performed). The presence of a redox reaction is indicated by current flowing through the cell. The voltage scan is then reversed and the redox reaction is reversed. The reference can be an external electrode, such as Ag/AgCl or SCE, or it can be an internal one, such as ferrocene, which has a known oxidation potential. The latter is often preferred for organic solvents, since the common reference electrodes are water based. A useful parameter that may come from cyclic voltammetry is the carrier gap. If both the reduction and oxidation are reversible, one can determine the energy difference between the hole and the electron (i.e. taking an electron out of the HOMO versus putting one into the LUMO). This value can be used to determine the LUMO energy from a well defined HOMO energy. Method for determining redox potentials and reversiblity of redox events using cyclic voltammetry is well known in the art.

UPS is an alternative technique for determining absolute binding energies in the solid state. Although solution electrochemistry is typically adequate for most compounds, and for giving relative redox potentials, the measurements taken in the solution phase can differ from values in the solid phase. A preferred method of estimating HOMO energies in the solid state is UPS. This is a photoelectric measurement, where the solid is irradiated with UV photons. The energy of the photons are gradually increased until photogenerated electrons are observed. The onset of ejected electrons gives the energy of the HOMO. The photons at that energy have just enough energy to eject an electron from the top of the filled levels. UPS provides HOMO energy level values in eV relative to vacuum which corresponds to the binding energy for the electron.

Inverse photoemission may be used to directly estimate LUMO energy levels. This technique involves pre-reducing the sample and then probing the filled states to estimate the LUMO energies. More specifically, a material is injected with electrons which then decay into unoccupied states and emit light. By varying the energy of the incoming electrons and the angle of the incident beam, electronic structure of a material can be studied. Methods of measuring LUMO energy levels using inverse photoemission are well known to those skilled in the art.

Optical gap values can be determined from the intersection of the normalized

absorption and emission spectra. For molecules that have very little structural rearrangement in going from the ground state to the excited, such that the gap between the absorption and emission λ_{max} values is rather small, the intersection energy is a good estimate of the optical gap (the 0-0 transition energy). Thus, the optical gap roughly corresponds to the HOMO-LUMO gap, and such estimation may be adequate for ideal systems. However, if the shift

5   between the absorption and emission maxima is large (Stokes shift) the optical gap can be more difficult to determine. For example, if there is a structural rearrangement in the excited state or the measured absorption does not represent the lowest energy excited state, then there can be a substantial error. Thus, for the selection of potential exciton blocking materials, the edge of the absorption band of the material is preferably used to obtain a value for its optical

10   gap. In this way, device layers comprising materials having absorption band energies higher than for adjacent layers may serve as effective exciton blocking layers. For example, if an exciton approaches a layer in a device having a higher energy absorption edge than the material containing the exciton, the probability that the exciton will be transferred into the higher energy material is low. For molecules emitting from triplet excited states, the

15   absorption edge is a preferred estimate for optical gap, since the intersystem crossing leads to a very large Stokes shift.

Light emitting devices of the present invention can be fabricated by a variety of techniques well known to those skilled in the art. Small molecule layers, including those comprised of neutral metal complexes, can be prepared by vacuum deposition, organic vapor

20   phase deposition (OVPD), such as disclosed in Application No. 08/972,156, filed November 17, 1997, which is incorporated herein by reference in it its entirety, or solution processing such as spin coating. Polymeric films can be deposited by spin coating and CVD. Layers of charged compounds, such as salts of charged metal complexes, can be prepared by solution methods such a spin coating or by an OVPD method such as disclosed in U.S. Pat.

25   No. 5,554,220, which is incorporated herein by reference in its entirety. Layer deposition generally, though not necessarily, proceeds in the direction of the anode to the cathode, and the anode typically rests on a substrate. As such, methods of fabricating devices, involving depositing a blocking layer that comprises a metal complex onto a preexisting layer, are also encompassed by the present invention. Preexisting layers include any layer that is designed

30   to be in contact with the blocking layer. In some embodiments, the preexisting layer can be

an emissive layer or a HTL. Devices and techniques for their fabrication are described throughout the literature and in, for example, U.S. Pat. Nos. 5,703,436; 5,986,401; 6,013,982; 6,097,147; and 6,166,489. For devices from which light emission is directed substantially out of the bottom of the device (i.e., substrate side), a transparent anode material such as ITO may be used as the bottom electron. Since the top electrode of such a device does not need

5   to be transparent, such a top electrode, which is typically a cathode, may be comprised of a thick and reflective metal layer having a high electrical conductivity. In contrast, for transparent or top-emitting devices, a transparent cathode may be used such as disclosed in U.S. Pat. Nos. 5,703,436 and 5,707,745, each of which is incorporated herein by reference in its entirety. Top-emitting devices may have an opaque and/or reflective substrate, such

10   that light is produced substantially out of the top of the device. Devices can also be fully transparent, emitting from both top and bottom.

Transparent cathodes, such as those used in top-emitting devices preferably have optical transmission characteristics such that the device has an optical transmission of at least about 50%, although lower optical transmissions can be used. In some embodiments, devices

15   include transparent cathodes having optical characteristics that permit the devices to have optical transmissions of at least about 70%, 85%, or more. Transparent cathodes, such as those described in U.S. Pat. Nos. 5,703,436 and 5,707,745, typically comprise a thin layer of metal such as Mg:Ag with a thickness, for example, that is less than about 100 Å. The Mg:Ag layer can be coated with a transparent, electrically-condutive, sputter-deposited, ITO

20   layer. Such cathodes are often referred to as compound cathodes or as TOLED (transparent-OLED) cathodes. The thickness of the Mg:Ag and ITO layers in compound cathodes may each be adjusted to produce the desired combination of both high optical transmission and high electrical conductivity, for example, an electrical conductivity as reflected by an overall cathode resistivity of about 30 to 100 ohms per square. However, even though such a

25   relatively low resistivity can be acceptable for certain types of applications, such a resistivity can still be somewhat too high for passive matrix array OLED pixels in which the current that powers each pixel needs to be conducted across the entire array through the narrow strips of the compound cathode.

The present invention further includes methods of facilitating hole transport in a light emitting device, wherein the light emitting device preferably comprises a hole transporting layer and an emissive layer, and wherein the hole transporting layer comprises at least one metal complex. In accordance with preferred embodiments of the methods, the device is designed such that the emissive layer has a higher HOMO energy level than the HOMO

5   energy level of the hole transporting layer. In some embodiments, the methods involve placing an electron blocking layer between the HTL and EL, where the HOMO energy level of the electron blocking layer has a HOMO energy level between that of the HTL and EL.

The present invention further includes methods of transporting holes in a hole transporting layer of a light emitting device, where said hole transporting layer comprises at

10   least one metal complex, comprising applying a voltage across a device of this structure.

Structures of light emitting devices are often referred to by a sequential listing of layer materials separated by slashes. For example, a device having an anode layer adjacent to a hole transporting which is adjacent to an emissive layer which is adjacent to an electron blocking layer which is adjacent to a cathode layer can be written as

15   anode/HTL/EL/ETL/cathode. As such, devices of the present invention can include the substructures HTL/EL/HBL, HTL/EBL/EL, HTL/EBL/ETL, an others. Some preferred structures of the present invention include anode/HTL/EL/HBL/ETL/cathode and anode/HTL/EBL/EL/ETL/cathode. Other embodiments include devices with substructures HTL/EL or HTL/EBL/EL where each of the EL, HTL, and EBL comprise at least one metal

20   complex or where none of the EL, HTL, or EBL comprise solely organic molecules. Further embodiments include a device, having a plurality of layers, devoid of a layer that is composed solely of organic molecules or a device having a plurality of layers where each of the layers contains at least one metal complex.

Light emitting devices of the present invention can be used in a pixel for a display.

25   Virtually any type of display can incorporate the present devices. Displays can include computer monitors, televisions, personal digital assistants, printers, instrument panels, bill boards, and the like. In particular, the present devices can be used in heads-up displays because they can be substantially transparent when not in use.

As those skilled in the art will appreciate, numerous changes and modifications can

30   be made to the preferred embodiments of the invention without departing from the spirit of

the invention. It is intended that all such variations fall within the scope of the invention.

Throughout this specification various groupings are employed to conveniently describe constituent variables of compounds and groups of various related moieties. It is specifically intended that each occurrence of such groups throughout this specification include every possible subcombination of the members of the groups, including the

5   individual members thereof.

It is intended that each of the patents, applications, and printed publications mentioned in this patent document be hereby incorporated by reference in their entirety.

EXAMPLES

10

Example 1: Synthesis of *Tris* (1-phenylpyrazole-C^2,N') cobalt (III)   (Co(ppz)$_3$)

To a solution of 1-phenylpyrazole (1.0 equiv. Mol, 6.93 mmol), in THF (3 ml), was added ethylmagnesium bromide (1.1 equiv. Mol, 7.6mmol). The reaction mixture was refluxed for three hours under argon atmosphere, and then cooled in a dry ice/acetone bath.

15   A solution of cobalt (II) bromide (0.5 equiv mol, 3.47mmol) in THF (8ml) was then added slowly to the Grignard. Immediately the reaction mixture turned black. The bath was removed and the mixture was stirred two days.

The reaction mixture was transferred to a separatory funnel containing aqueous NH$_4$Cl (10g/liter, 75ml) and CH$_2$Cl$_2$ (75ml) and shook. The resulting thick emulsion was

20   passed through a course fritted funnel, which aided the separation of the two layers. The organic layer was isolated and the aqueous layer was extracted twice more with CH$_2$Cl$_2$ (75ml). The CH$_2$Cl$_2$ solutions were combined, dried over MgSO$_4$, filtered and concentrate under reduced pressure. Addition of hexanes to the black/yellow concentrate caused the product to precipitate as a dark yellow solid. ^{1}H NMR analysis indicated that the crude

25   product was a mixture of facial and meridonal isomers, as well as a small amount of impurities. An attempt was made to separate the two isomers and impurities by column chromatography, using silica gel and 1:1 CH$_2$Cl$_2$: toluene eluent. Only the facial isomer exited the column, whereas the meridonal isomer stuck to the silica and soon after turned purple in color.

30

Example 2: Synthesis of *Tris* (1-(4-tolylphenyl)pyrazole-C^2,N') cobalt (III) (CoMPPZ)

        Ligand synthesis (4-tolylphenylpyrazole):   A 250ml flask was charged with a magnetic stirrer bar, 4-tolylboronic acid (16mmol, 2.0equiv.), pyrazole (8mmol, 1.0equiv.), anhydrous cupric acetate (12mmol, 1.5mmol), 6g activated 4Å molecular sieves, pyridine (16mmol, 2.0equiv.), and 96 ml dichloromethane. The reaction was stirred under air at

5   ambient temperature in a loosely capped flask for 2 days. The reaction mixture was filtered through Celite, washed with water and purified by silica gel chromatography (eluent: ethyl acetate: hexane=1:7)

        Complex synthesis: To a solution of 4-tolyllpyrazole (1.0 equiv. Mol, 6.93mmol), in THF (3ml), was added ethylmagnesium bromide (1.1 equiv. Mol, 7.6mmol). The reaction

10   mixture was refluxed for three hours under argon atmosphere, and then cooled in a dry ice/acetone bath. A solution of cobalt (II) bromide (0.5 equiv mol, 3.47mmol) in THF (8ml) was then added slowly to the Grignard. Immediately the reaction mixture turned black. The bath was removed and the mixture was stirred two days.

        The reaction mixture was transferred to a separatory funnel containing aqueous

15   NH$_4$Cl (10g/liter, 75ml) and CH$_2$Cl$_2$ (75ml) and shook. The resulting thick emulsion was passed through a course fritted funnel, which aided the separation of the two layers. The organic layer was isolated and the aqueous layer was extracted twice more with CH$_2$Cl$_2$ (75ml). The CH$_2$Cl$_2$ solutions were combined, dried over MgSO$_4$, filtered and concentrate under reduced pressure. Addition of hexanes to the black/yellow concentrate caused the

20   product to precipitate as a dark yellow solid. ^{1}H NMR analysis indicated that the crude product was a mixture of facial and meridonal isomers, as well as a small amount of impurities. An attempt was made to separate the two isomers and impurities by column chromatography, using silica gel and 1:1 CH$_2$Cl$_2$: toluene eluent. Only the facial isomer exited the column, whereas the meridonal isomer stuck to the silica and soon after turned

25   purple in color.

Example 3:   Synthesis of *Tris* (1-(4-methoxyphenyl)pyrazole-C^2,N') cobalt (III) (CoMOPPZ)

        Ligand synthesis (4-methoxyphenylpyrazole):   A 250ml flask was charged with

30   a magnetic stirrer bar, 4-methoxyboronic acid (16mmol, 2.0equiv.), pyrazole (8mmol,

1.0equiv.), anhydrous cupric acetate (12mmol, 1.5mmol), 6g activated 4Å molecular sieves, pyridine (16mmol, 2.0equiv.), and 96 ml dichloromethane. The reaction was stirred under air at ambient temperature in a loosely capped flask for 2 days. The reaction mixture was filtered through Celite, washed with water and purified by silica gel chromatography (eluent: ethyl acetate: hexane=1:7)

5   Complex synthesis: To a solution of 4-methoxypyrazole (1.0 equiv. Mol, 6.93mmol), in THF (3ml), was added ethylmagnesium bromide (1.1 equiv. Mol, 7.6mmol). The reaction mixture was refluxed for three hours under argon atmosphere, and then cooled in a dry ice/acetone bath. A solution of cobalt (II) bromide (0.5 equiv mol, 3.47mmol) in THF (8ml) was then added slowly to the Grignard. Immediately the reaction mixture turned

10   black. The bath was removed and the mixture was stirred two days.

The reaction mixture was transferred to a separatory funnel containing aqueous NH_4Cl (10g/liter, 75ml) and CH_2Cl_2 (75ml) and shook. The resulting thick emulsion was passed through a course fritted funnel, which aided the separation of the two layers. The organic layer was isolated and the aqueous layer was extracted twice more with CH_2Cl_2

15   (75ml). The CH_2Cl_2 solutions were combined, dried over $MgSO_4$, filtered and concentrate under reduced pressure. Addition of hexanes to the black/yellow concentrate caused the product to precipitate as a dark yellow solid. ^1H NMR analysis indicated that the crude product was a mixture of facial and meridonal isomers, as well as a small amount of impurities. An attempt was made to separate the two isomers and impurities by column

20   chromatography, using silica gel and 1:1 CH_2Cl_2: toluene eluent. Only the facial isomer exited the column, whereas the meridonal isomer stuck to the silica and soon after turned purple in color.

Example 4: Synthesis of *Tris* (1-(4,5-difluorophenyl)pyrazole-C^2,N') cobalt (III)

25   **(CodFPPZ)**

Ligand synthesis (4,5-difluorophenylpyrazole):   A 250ml flask was charged with a magnetic stirrer bar, 4,5-difluoroboronic acid (16mmol, 2.0equiv.), pyrazole (8mmol, 1.0equiv.), anhydrous cupric acetate (12mmol, 1.5mmol), 6g activated 4Å molecular sieves, pyridine (16mmol, 2.0equiv.), and 96 ml dichloromethane. The reaction was stirred under

30   air at ambient temperature in a loosely capped flask for 2 days. The reaction mixture was

filtered through Celite, washed with water and purified by silica gel chromatography (eluent: ethyl acetate: hexane=1:7)

Complex synthesis: To a solution of 4,5-difluoropyrazole (1.0 equiv. Mol, 6.93mmol), in THF (3ml), was added ethylmagnesium bromide (1.1 equiv. Mol, 7.6mmol). The reaction mixture was refluxed for three hours under argon atmosphere, and then cooled

5   in a dry ice/acetone bath. A solution of cobalt (II) bromide (0.5 equiv mol, 3.47mmol) in THF (8ml) was then added slowly to the Grignard. Immediately the reaction mixture turned black. The bath was removed and the mixture was stirred two days.

The reaction mixture was transferred to a separatory funnel containing aqueous NH_4Cl (10g/liter, 75ml) and CH_2Cl_2 (75ml) and shook. The resulting thick emulsion was

10   passed through a course fritted funnel, which aided the separation of the two layers. The organic layer was isolated and the aqueous layer was extracted twice more with CH_2Cl_2 (75ml). The CH_2Cl_2 solutions were combined, dried over $MgSO_4$, filtered and concentrate under reduced pressure. Addition of hexanes to the black/yellow concentrate caused the product to precipitate as a dark yellow solid. ^1H NMR analysis indicated that the crude

15   product was a mixture of facial and meridonal isomers, as well as a small amount of impurities. An attempt was made to separate the two isomers and impurities by column chromatography, using silica gel and 1:1 CH_2Cl_2: toluene eluent. Only the facial isomer exited the column, whereas the meridonal isomer stuck to the silica and soon after turned purple in color.

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Example 5: Synthesis of *Tris* (1-(4-fluorophenyl)pyrazole-C^2,N') cobalt (III) (CoFPPZ)

Ligand synthesis (4-fluorophenylpyrazole):   A 250ml flask was charged with a magnetic stirrer bar, 4-fluoroboronic acid (16mmol, 2.0equiv.), pyrazole (8mmol, 1.0equiv.), anhydrous cupric acetate (12mmol, 1.5mmol), 6g activated 4Å molecular sieves, pyridine

25   (16mmol, 2.0equiv.), and 96 ml dichloromethane. The reaction was stirred under air at ambient temperature in a loosely capped flask for 2 days. The reaction mixture was filtered through Celite, washed with water and purified by silica gel chromatography (eluent: ethyl acetate: hexane=1:7)

Complex synthesis: To a solution of 4-fluoropyrazole (1.0 equiv. Mol,

30   6.93mmol), in THF (3ml), was added ethylmagnesium bromide (1.1 equiv. Mol, 7.6mmol).

The reaction mixture was refluxed for three hours under argon atmosphere, and then cooled in a dry ice/acetone bath. A solution of cobalt (II) bromide (0.5 equiv mol, 3.47mmol) in THF (8ml) was then added slowly to the Grignard. Immediately the reaction mixture turned black. The bath was removed and the mixture was stirred two days.

5   The reaction mixture was transferred to a separatory funnel containing aqueous NH$_4$Cl (10g/liter, 75ml) and CH$_2$Cl$_2$ (75ml) and shook. The resulting thick emulsion was passed through a course fritted funnel, which aided the separation of the two layers. The organic layer was isolated and the aqueous layer was extracted twice more with CH$_2$Cl$_2$ (75ml). The CH$_2$Cl$_2$ solutions were combined, dried over MgSO$_4$, filtered and concentrate under reduced pressure. Addition of hexanes to the black/yellow concentrate caused the

10   product to precipitate as a dark yellow solid. ^{1}H NMR analysis indicated that the crude product was a mixture of facial and meridonal isomers, as well as a small amount of impurities. An attempt was made to separate the two isomers and impurities by column chromatography, using silica gel and 1:1 CH$_2$Cl$_2$: toluene eluent. Only the facial isomer exited the column, whereas the meridonal isomer stuck to the silica and soon after turned

15   purple in color.

Example 6: Synthesis of *Tris* (1-(4-*tert*-butylphenyl)pyrazole-C^2,N') cobalt (III) (CoBPPZ)

Ligand synthesis (4-*tert*-phenylpyrazole):   A 250ml flask was charged with a
20   magnetic stirrer bar, 4-*tert*-boronic acid (16mmol, 2.0equiv.), pyrazole (8mmol, 1.0equiv.), anhydrous cupric acetate (12mmol, 1.5mmol), 6g activated 4Å molecular sieves, pyridine (16mmol, 2.0equiv.), and 96 ml dichloromethane. The reaction was stirred under air at ambient temperature in a loosely capped flask for 2 days. The reaction mixture was filtered through Celite, washed with water and purified by silica gel chromatography (eluent: ethyl
25   acetate: hexane=1:7)

Complex synthesis: To a solution of 4-*tert*-pyrazole (1.0 equiv. Mol, 6.93mmol), in THF (3ml), was added ethylmagnesium bromide (1.1 equiv. Mol, 7.6mmol). The reaction mixture was refluxed for three hours under argon atmosphere, and then cooled in a dry ice/acetone bath. A solution of cobalt (II) bromide (0.5 equiv mol, 3.47mmol) in THF (8ml)

was then added slowly to the Grignard. Immediately the reaction mixture turned black. The bath was removed and the mixture was stirred two days.

The reaction mixture was transferred to a separatory funnel containing aqueous NH$_4$Cl (10g/liter, 75ml) and CH$_2$Cl$_2$ (75ml) and shook. The resulting thick emulsion was passed through a course fritted funnel, which aided the separation of the two layers. The

5   organic layer was isolated and the aqueous layer was extracted twice more with CH$_2$Cl$_2$ (75ml). The CH$_2$Cl$_2$ solutions were combined, dried over MgSO$_4$, filtered and concentrate under reduced pressure. Addition of hexanes to the black/yellow concentrate caused the product to precipitate as a dark yellow solid. ^{1}H NMR analysis indicated that the crude product was a mixture of facial and meridonal isomers, as well as a small amount of

10 impurities. An attempt was made to separate the two isomers and impurities by column chromatography, using silica gel and 1:1 CH$_2$Cl$_2$: toluene eluent. Only the facial isomer exited the column, whereas the meridonal isomer stuck to the silica and soon after turned purple in color.

15 **Example 7: Synthesis of Ga(III)tris[2-(((pyrrole-2-yl)methylidene)amino)ethyl]amine (Ga(pma)$_3$)**

The ligand [(((pyrrole-2-yl)methylidene)amino)ethyl]amine was prepared by adding a methanolic solution of pyrrole-2-carboxaldehyde (1.430 g, 15 mmol, 100 mL) to a methanolic solution of tris(2-aminoethyl)amine (0.720 g, 5 mmol, 10 mL). The resulting

20 yellow solution was stirred at room temperature for 30 min. A methanolic solution of gallium(III) nitrate hydrate (1.280 g, 5 mmol, 150 mL) was added to the ligand solution and stirred at room temperature for 30 min. The solution was filtered and left to stand at ambient temperature until crystallization occurred. The crude material was then sublimed at 235 °C.

25 **Example 8: Devices of the present invention.**

Functional OLEDs were prepared with the structure ITO/HTL/Alq$_3$/MgAg where Co(ppz)$_3$ was used as the HTL. These devices had lower efficiency than for comparable devices in which the HTL was composed of triarylamines. Higher efficiencies were achieved for these devices when a thin layer of NPD was inset between the Co(ppz)$_3$ and Alq$_3$ layers.

The HOMO levels for both NPD and Co(ppz)$_3$ are at comparable energies (5.5 eV for NPD and 5.4 eV for Co(ppz)$_3$). See Figures 13-15.

Example 9: Devices according to embodiments of the present invention.

Functional OLEDs were prepared with a Co(ppz)$_3$ hole transporting layer, a Ga(pma)$_3$ electron blocking layer and an Alq$_3$ emissive layer. The turn on voltage was roughly 3.5 V (voltage at which external brightness = Cd/m^2), and the peak efficiency was greater than 1.2%. See Figures 7-10.

Example 10: Devices according to embodiments of the present invention

Functional OLEDs were prepared with a Co(ppz)$_3$/Ga(pma)$_3$ hole tranporting layer and a doped CBP emissive layer. An analogous device was also prepared with an NPD hole transporting layer. Overall, the Co(ppz)$_3$/(Ga(pma)$_3$ device performed better than the device with the NPD layer. The low voltage currents are lower and the spectra show no blue emission (below 400 nm) for Co(ppz)$_3$/(Ga(pma)$_3$. The turn-on voltages for the Co(ppz)$_3$/(Ga(pma)$_3$ based device was slightly higher than for the NPD-based device and the quantum efficiency was lower. Both of these parameters are expected to improve with device optimization. See Figures 11-12.

What is claimed is:

1.   A light emitting device comprising a hole transporting layer, wherein said hole transporting layer comprises at least one metal complex.

2.   The light emitting device of claim 1 wherein said hole transporting layer consists essentially of said metal complex.

3.   The light emitting device of claim 1 wherein said hole transporting layer comprises an organic matrix doped with said metal complex.

4.   The light emitting device of claim 1 wherein said metal complex is coordinatively saturated.

5.   The light emitting device of claim 1 wherein said metal complex has a coordination number of six.

6.   The light emitting device of claim 1 wherein said metal complex has a coordination number of four.

7.   The light emitting device of claim 1 wherein said metal of said metal complex is a transition metal.

8.   The light emitting device of claim 7 wherein said transition metal is a first row transition metal.

9.   The light emitting device of claim 7 wherein said transition metal is a second or third row transition metal.

10.   The light emitting device of claim 1 wherein the metal of said metal complex is Fe, Co, Ru, Pd, Os or Ir.

11.   The light emitting device of claim 1 wherein the metal of said metal complex is Fe or Co.

12.   The light emitting device of claim 1 wherein the metal of said metal complex is Fe.

13.   The light emitting device of claim 1 wherein the metal of said metal complex is Co.

14.   The light emitting device of claim 1 wherein said metal complex has one of the formulas I or II:

I   II

wherein:

M' and M''' are each, independently, a metal atom;

R_{10}, R_{13}, R_{20} and R_{21} are each, independently, N or CH;

R_{11} and R_{12} are each, independently, N, CH, O or S;

Ring systems A, B, G, K and L are each independently a mono-, di- or tricyclic fused aliphatic or aromatic ring system optionally containing up to 5 hetero atoms;
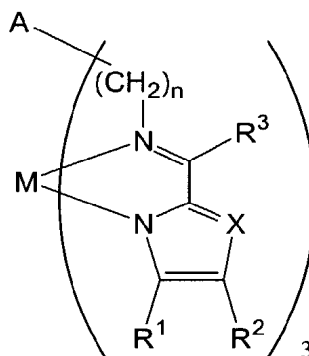
Z is C_1-C_6 alkyl, C_2-C_8 mono- or poly alkenyl, C_2-C_8 mono- or poly alkynyl, or a bond; and

Q is BH, N, or CH.

15.   The light emitting device of claim 14 wherein said metal complex has the formula I.

16.   The light emitting device of claim 15 wherein said metal complex has the formula I and wherein Ring system A and Ring system B are each monocyclic.

17.   The light emitting device of claim 16 wherein said metal complex has the formula I, Ring system A is a five membered heteroaryl monocyclic ring and Ring system B is a six membered aryl or heteroaryl monocyclic ring.

18.   The light emitting device of claim 17 wherein R_{10} and R_{11} are N, and R_{13} is CH.

19.   The light emitting device of claim 17 wherein Ring A forms pyrazole.

20.   The light emitting device of claim 17 wherein Ring B forms phenyl.

21.   The light emitting device of claim 14 wherein said metal is a d^0, d^1, d^2,d^3,d^4,d^5, or d^6 metal.

22.   The light emitting device of claim 14 wherein M′ is a transition metal.

23.   The light emitting device of claim 14 wherein M′ is Fe, Co, Ru, Pd, Os or Ir.

24.   The light emitting device of claim 14 wherein M′ is Fe or Co.

25.   The light emitting device of claim 14 wherein M′ is Co.

26.   The light emitting device of claim 14 wherein M′ is Fe.

27.   The light emitting device of claim 1 wherein said metal complex is Co(ppz)$_3$.

28.   The light emitting device of claim 14 wherein said metal complex has the formula II.

29.   The light emitting device of claim 14 wherein said metal atom complex has the formula II and wherein Ring systems G, K and L are each 5 or 6 member monocyclic rings.

30.   The light emitting device of claim 29 wherein Ring systems G, K and L are each 5-membered heteroaryl monocyclic rings.

31.   The light emitting device of claim 30 wherein R_{21} and R_{22} are each N.

32.   The light emitting device of claim 31 wherein ring systems G, K and L each form pyrazole.

33.   The light emitting device of claim 28 wherein M$'''$ is a $d^{5/6}$ or $d^{2/3}$ metal.

34.   The light emitting device of claim 28 wherein M$'''$ is a transition metal.

35.   The light emitting device of claim 28 wherein M$'''$ is Fe, Co, Ru, Pd, Os or Ir.

36.   The light emitting device of claim 28 wherein M$'''$ is Fe or Co.

37.   The light emitting device of claim 14 wherein M$'''$ is Fe.

38.   The light emitting device of claim 1 wherein said metal complex is FeTp'$_2$.

39.   The light emitting device of claim 1 further comprising an electron blocking layer.

40.   The light emitting device of claim 39 wherein said electron blocking layer comprises an organic electron blocking material.

41.   The light emitting device of claim 40 wherein said organic electron blocking material is selected from triarylamines or benzidenes.

42.   The light emitting device of claim 39 wherein said electron blocking layer comprises a metal complex.

43.   The light emitting device of claim 42 wherein said electron blocking layer consists essentially of said metal complex.

44.   The light emitting device of claim 42 wherein said electron blocking layer comprises a matrix doped with said metal complex.

45.   The light emitting device of claim 42 wherein said electron blocking layer has a HOMO energy level close to the HOMO energy level of said hole transporting layer.

46.   The light emitting device of claim 42 wherein said electron blocking layer has a HOMO energy level higher than the HOMO energy level of said hole transporting layer.

47.   The light emitting device of claim 42 wherein said metal complex of said electron blocking layer comprises a metal selected from Ga, In, Sn, or a group 8, 9, or 10 transition metal.

48.   The light emitting device of claim 42 wherein said metal complex of said electron blocking layer comprises Ga.

49.   The light emitting device of claim 42 wherein said metal complex of said electron blocking layer comprises a multidentate ligand.

50.   The light emitting device of claim 49 wherein said multidentate ligand has a bridging atom selected from N and P.

51.   The light emitting device of claim 49 wherein said multidentate ligand has a mesityl bridge moiety.

52.   The light emitting device of claim 49 wherein said multidentate ligand comprises up to three mono-, bi- or tricyclic heteroaromatic moieties.

53.   The light emitting device of claim 1 further comprising an electron blocking layer comprising a compound having the formula:

wherein:

M is a metal atom;

X is N or CX' where X' is H, C_1-C_{20} alkyl, C_2-C_{40} mono- or poly alkenyl, C_2-C_{40} mono- or poly alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or halo;

A is CH, CX', N, P, P(=O), aryl or heteroaryl;

each R^1 and R^2 is, independently, H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or halo; or

R^1 and R^2, together with the carbon atoms to which they are attached, link to form a fused C_3-C_8 cycloalkyl or aryl group;

R^3 is H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or halo; and

n is 1 to 5.

54.   The light emitting device of claim 53 wherein

M is a trivalent metal atom;

X is CH or N;

A is N or 1,3, 5-phenyl;

each R^1 and R^2 are H, or R^1 and R^2, together with the carbon atoms to which they are attached, link to form a phenyl group;

R^3 is H; and

n is 1 or 2.

55.   The light emitting device of claim 53 wherein M is Ga.

56.   The light emitting device of claim 53 wherein said electron blocking layer comprises Ga(pma)$_3$.

57.   The light emitting device of claim 53 wherein said metal complex of said hole transporting layer is Co(ppz)$_3$.

58.   The light emitting device of claim 53 wherein said metal complex of said hole transporting layer is FeTp'$_2$.

59.   A light emitting device comprising the substructure HTL/EL or HTL/EBL/EL; wherein each of said EL, HTL, and EBL comprise at least one metal complex.

60.   A light emitting device comprising the substructure HTL/EL or HTL/EBL/EL; wherein none of said EL, HTL, or EBL is comprised solely of organic molecules.

61.   A light emitting device having a plurality of layers, said device being devoid of a layer that is composed solely of organic molecules.

62.   The light emitting device of claim 61 wherein each of said layers contains at least one metal complex.

63.   A light emitting device comprising a hole transporting layer, an emissive layer, and a blocking layer;

said hole transporting layer having a first HOMO energy, wherein said hole transporting layer comprises at least one metal complex;

said emissive layer comprising at least one material capable of transporting electrons, said material having a second HOMO energy; and

said blocking layer comprising a material having a HOMO energy that is between said first and second HOMO energies.

64.   The device of claim 63 wherein said blocking layer resides between said hole transporting layer and said emissive layer.

65.   The device of claim 63 wherein said blocking layer comprises an organic electron blocking material.

66.   The light emitting device of claim 65 wherein said organic electron blocking material is selected from triarylamines or benzidenes.

67.   The light emitting device of claim 63 wherein said electron blocking layer comprises a metal complex.

68. A method of facilitating hole transport in a light emitting device, said light emitting device comprising a hole transporting layer and an emissive layer;

said hole transporting layer comprising at least one metal complex and having a first HOMO energy;

said emissive layer comprising at least one material capable of transporting electrons, said material having a second HOMO energy higher than said HOMO energy of said hole transporting layer;

said method comprising the step of placing a blocking layer between said hole transporting layer and said emissive layer, wherein said blocking layer comprises a material having a HOMO energy level that is between said first and second HOMO energies.

69. The method of claim 68 wherein said metal complex of said hole transporting layer is a complex formula I or II:

I   II

wherein:

M' and M''' are each, independently, a metal atom;

R_{10}, R_{13}, R_{20} and R_{21} are each, independently, N or CH;

R_{11} and R_{12} are each, independently, N, CH, O or S;

Ring systems A, B, G, K and L are each independently a mono-, di- or tricyclic fused aliphatic or aromatic ring system optionally containing up to 5 hetero atoms;

Z is C_1-C_6 alkyl, C_2-C_8 mono- or poly alkenyl, C_2-C_8 mono- or poly alkynyl, or a bond; and

Q is BH, N, or CH.

70.   The method of claim 68 wherein said metal complex of said hole transporting layer is $Co(ppz)_3$ or $FeTp'_2$.

71.   The method of claim 68 wherein said blocking layer comprises at least one metal complex.

72.   The method of claim 71 wherein said metal complex of said blocking layer is a compound having the formula:

wherein:

M is a metal atom;

X is N or CX' where X' is H, C_1-C_{20} alkyl, C_2-C_{40} mono- or poly alkenyl, C_2-C_{40} mono- or poly alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or halo;

A is CH, CX', N, P, P(=O), aryl or heteroaryl;

each R^1 and R^2 is, independently, H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or halo; or

R^1 and R^2, together with the carbon atoms to which they are attached, link to form a fused C_3-C_8 cycloalkyl or aryl group;

R^3 is H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or halo; and

n is 1 to 5. .

73. The method of claim 71 wherein said metal complex of said blocking layer is $Ga(pma)_3$.

74. The method of claim 68 wherein said hole transporting layer comprises $Co(ppz)_3$ or $FeTp'_2$, and said barrier layer comprises $Ga(pma)_3$.

75. A method of fabricating a light emitting device, said method comprising placing a hole transporting layer in electrical contact with an emissive layer, wherein said hole transporting layer comprises a compound of formulas I or II:

I   II

wherein:

M' and M''' are each, independently, a metal atom;

R_{10}, R_{13}, R_{20} and R_{21} are each, independently, N or CH;

R_{11} and R_{12} are each, independently, N, CH, O or S;

Ring systems A, B, G, K and L are each independently a mono-, di- or tricyclic fused aliphatic or aromatic ring system optionally containing up to 5 hetero atoms;

Z is C_1-C_6 alkyl, C_2-C_8 mono- or poly alkenyl, C_2-C_8 mono- or poly alkynyl, or a bond; and

Q is BH, N, or CH.

76.   The method of claim 75 wherein said light emitting device further comprises an electron blocking layer.

77.   The method of claim 76 wherein said electron blocking layer comprises a compound having the formula:

wherein:

M is a metal atom;

X is N or CX' where X' is H, C_1-C_{20} alkyl, C_2-C_{40} mono- or poly alkenyl, C_2-C_{40} mono- or poly alkynyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, or halo;

A is CH, CX', N, P, P(=O), aryl or heteroaryl;

each R^1 and R^2 is, independently, H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or halo; or

R^1 and R^2, together with the carbon atoms to which they are attached, link to form a fused C_3-C_8 cycloalkyl or aryl group;

R^3 is H, C_1-C_{20} alkyl, C_2-C_{40} alkenyl, C_2-C_{40} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or halo; and

n is 1 to 5.

78.   The method of claim 76 wherein said electron blocking layer comprises Ga(pma)$_3$.

79.   The method of claim 75 wherein said compound is Co(ppz)$_3$ or FeTp'$_2$.

80.   The method of claim 75 wherein said compound is Co(ppz)$_3$.

81.   A method of transporting holes in a hole transporting layer of a light emitting device, wherein said hole transporting layer comprises at least one metal complex, said method comprising applying a voltage across said device.

82.   A pixel comprising the light emitting device of claim 1.

83.   A pixel comprising the light emitting device of claim 14.

84.   A pixel comprising the light emitting device of claim 27.

85.   A pixel comprising the light emitting device of claim 38.

86.   A pixel comprising the light emitting device of claim 53.

87.   A pixel comprising the light emitting device of claim 63.

88.   An electronic display comprising the light emitting device of claim 1.

89.   An electronic display comprising the light emitting device of claim 14.

90.   An electronic display comprising the light emitting device of claim 27.

91.   An electronic display comprising the light emitting device of claim 38.

92.   An electronic display comprising the light emitting device of claim 53.

93.   An electronic display comprising the light emitting device of claim 63.

FIGURE 1

FIGURE 2

FIGURE 3
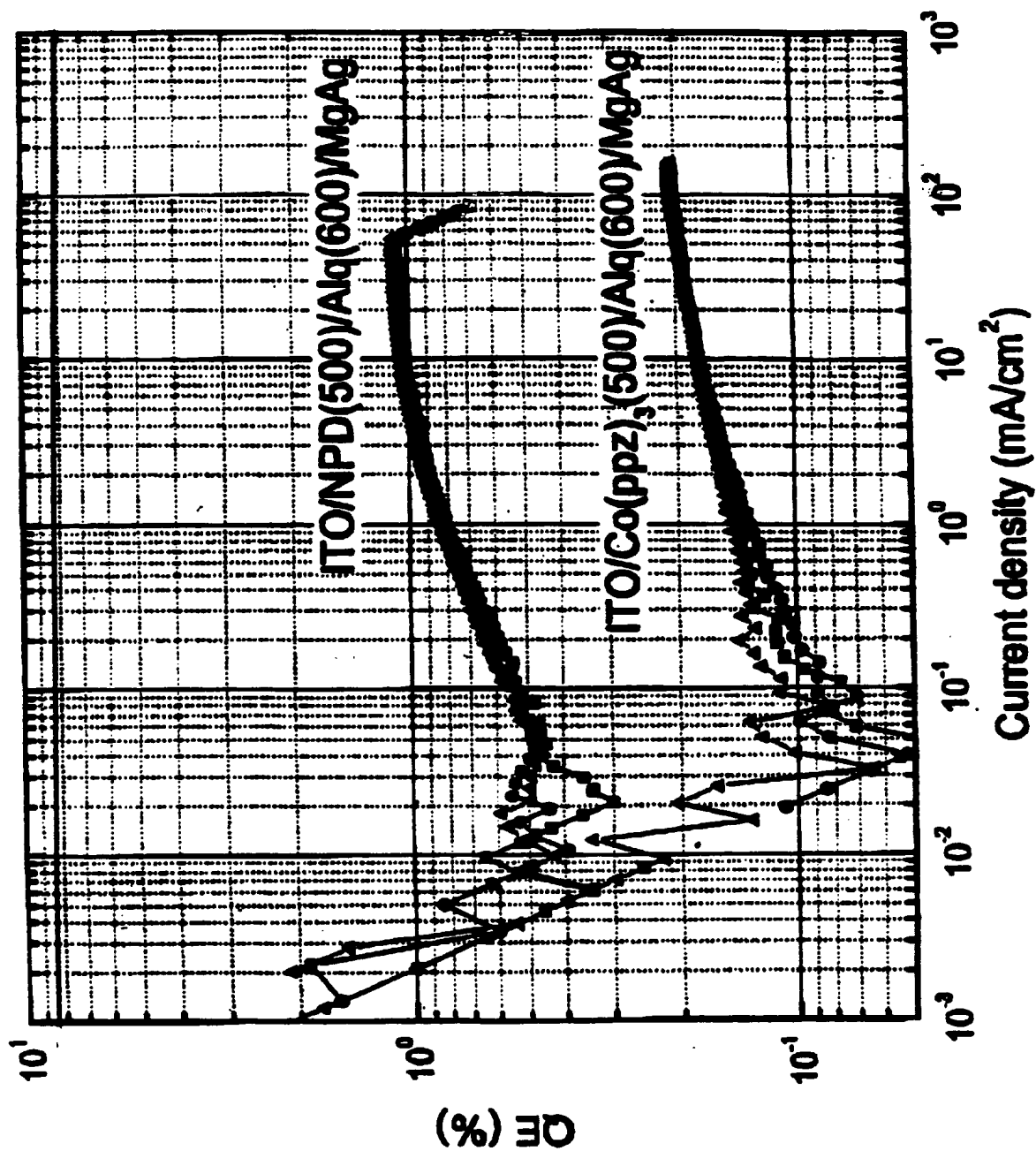
FIGURE 4A
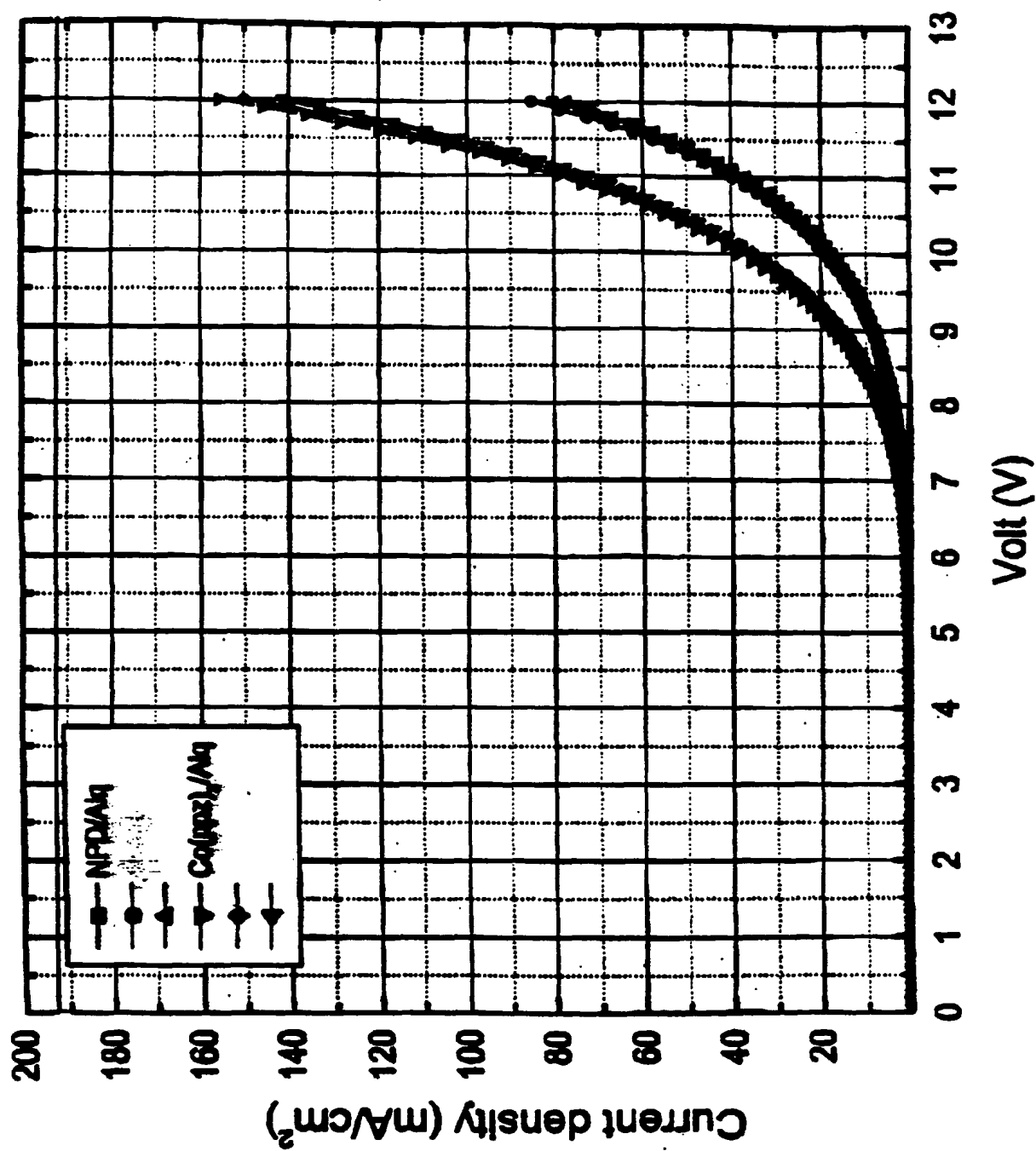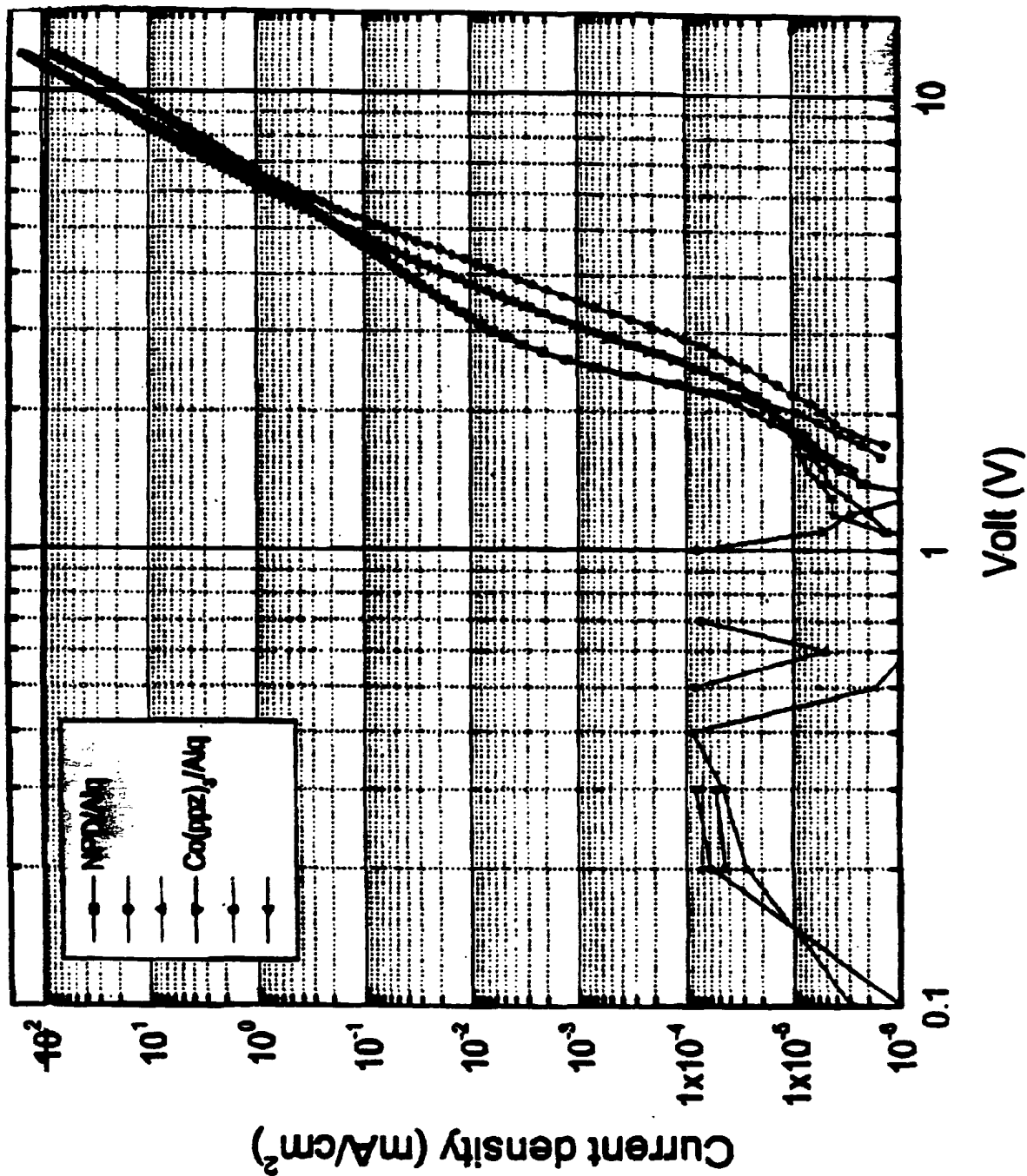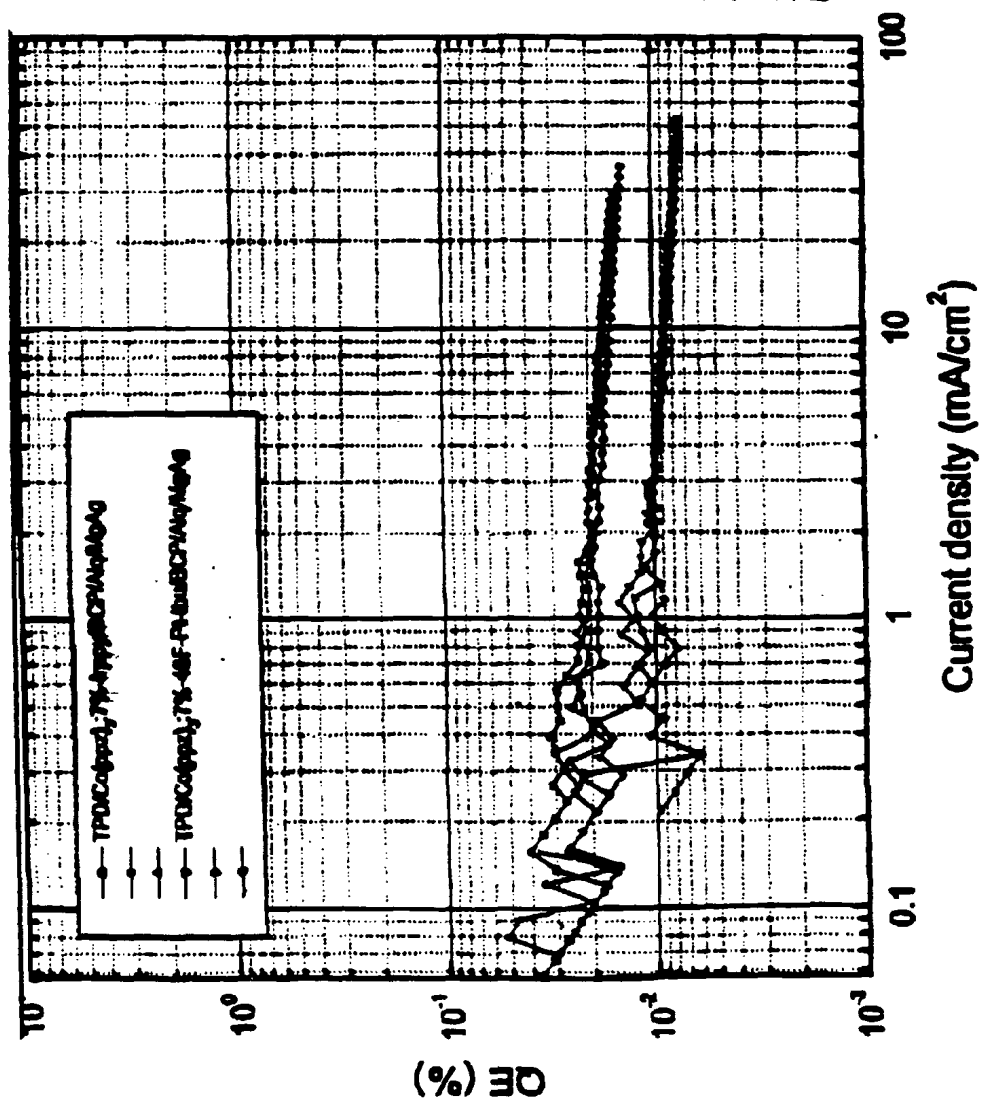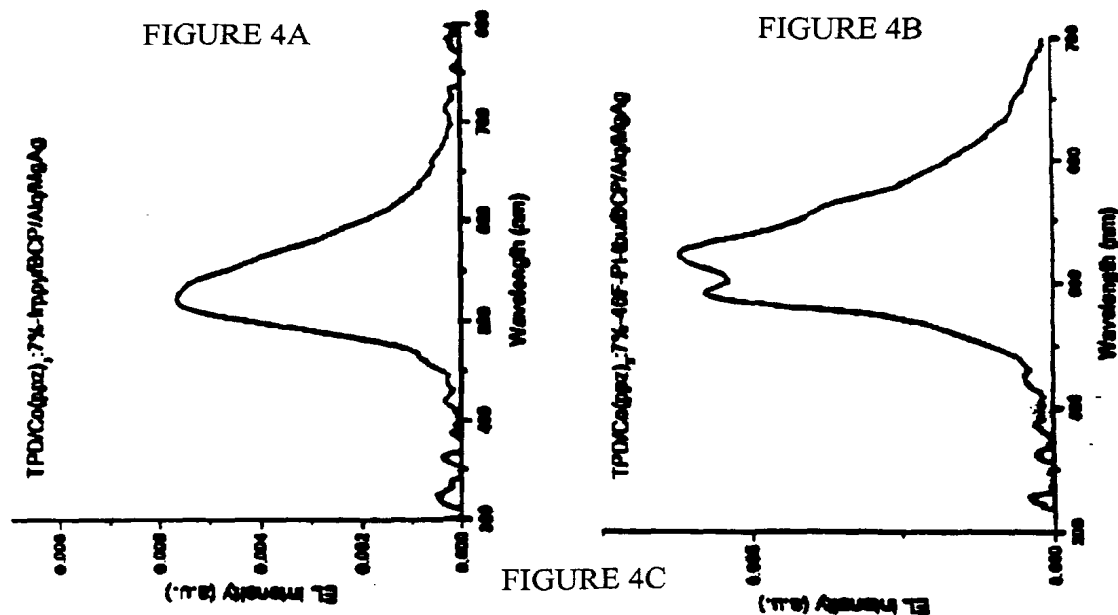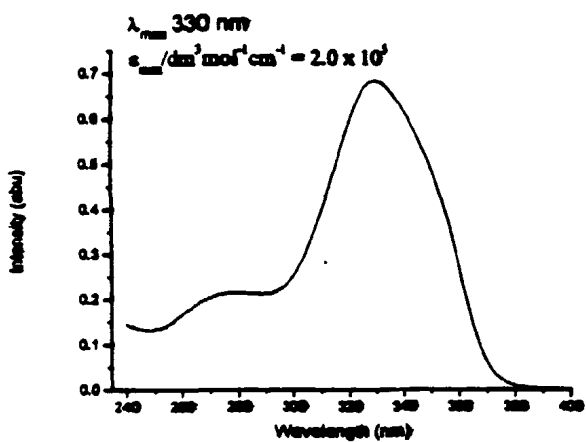
FIGURE 4B

FIGURE 4C

FIGURE 5

FIGURE 6A   FIGURE 6B
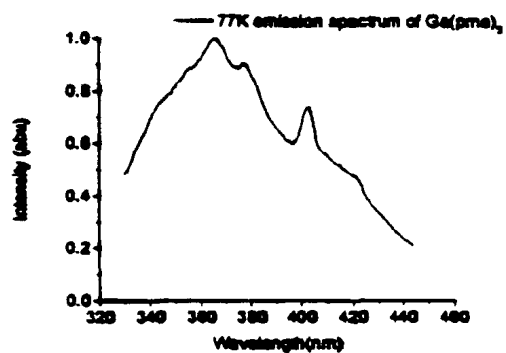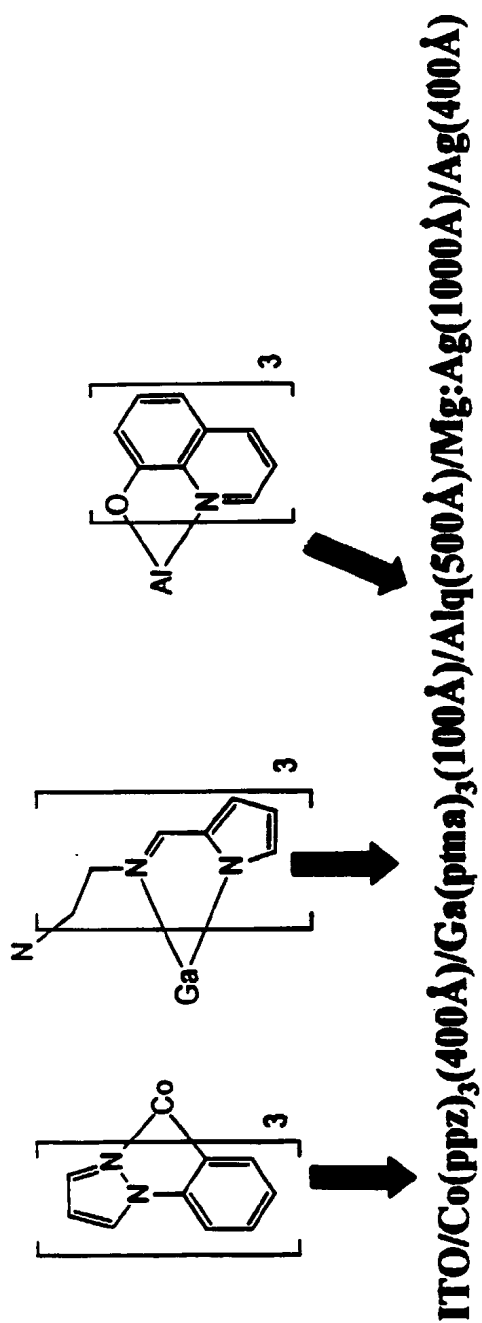
FIGURE 7
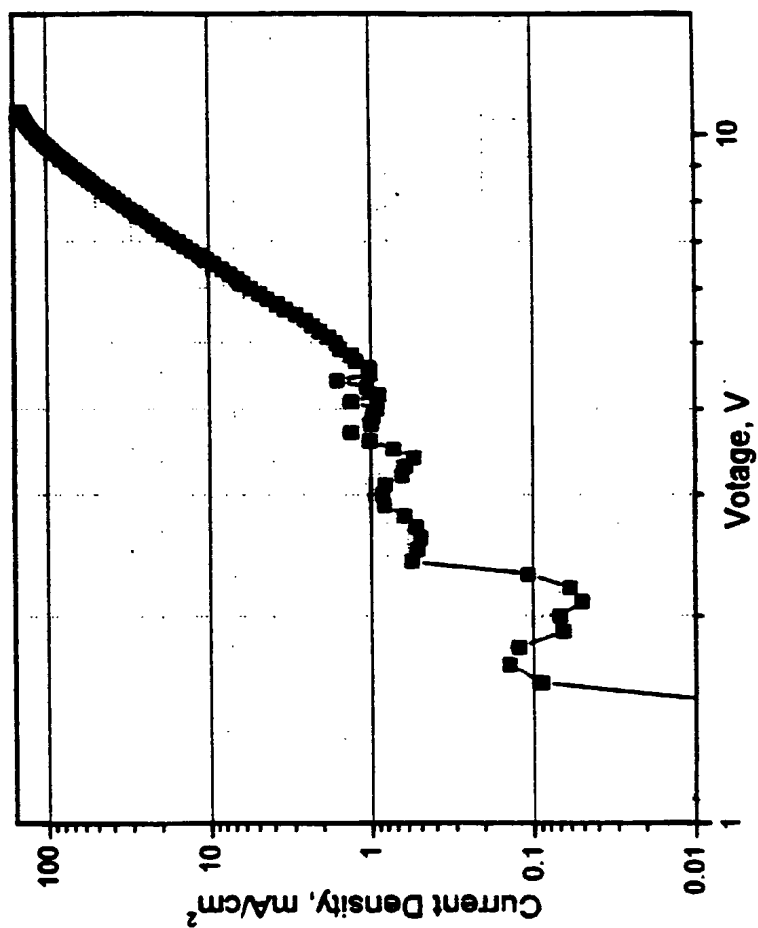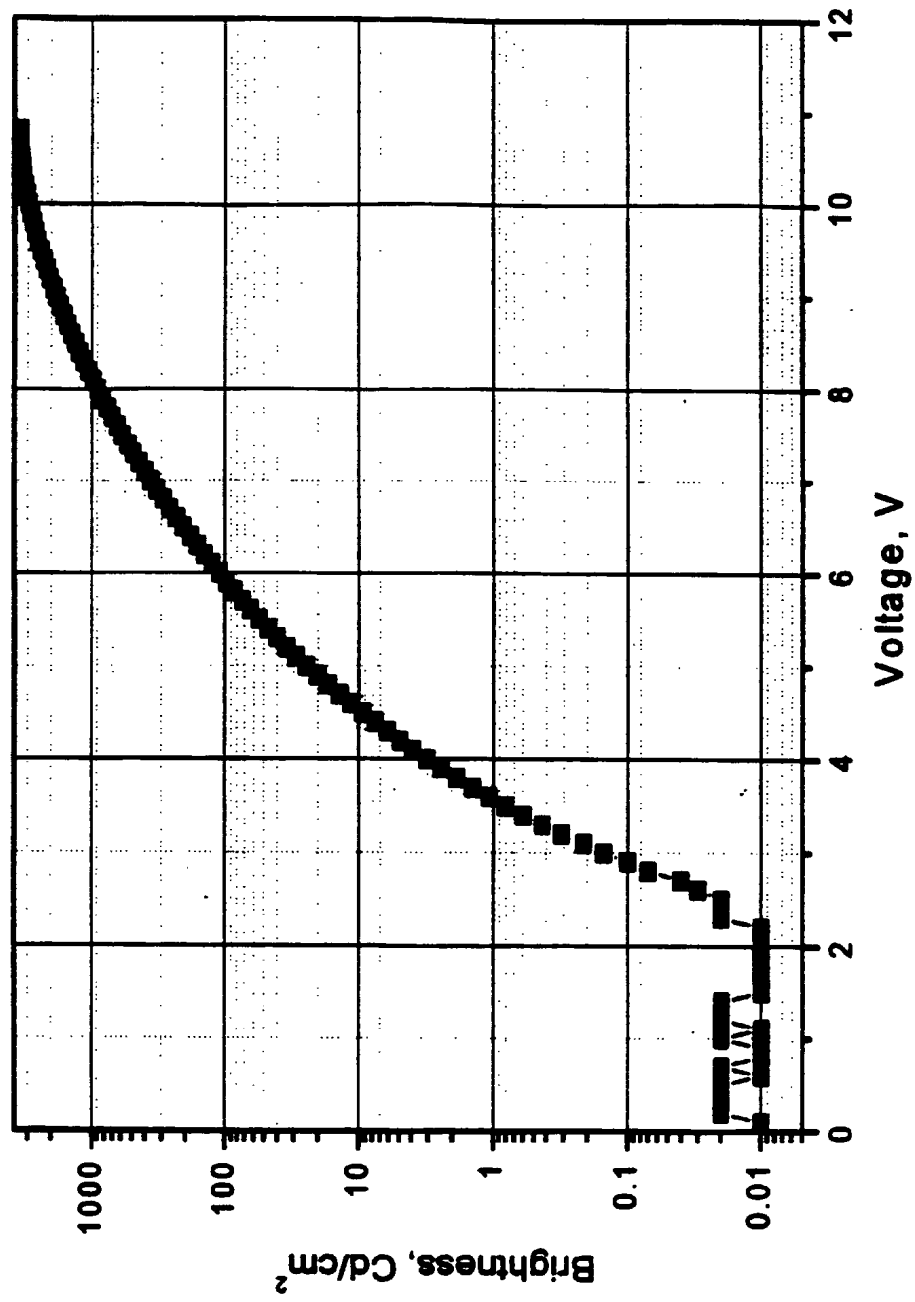
FIGURE 8

ITO/Co(ppz)₃(400Å)/Ga(pma)₃(100Å)/Alq(500Å)/Mg:Ag(1000Å)/Ag(400Å)

FIGURE 9

ITO/Co(ppz)₃(400Å)/Ga(pma)₃(100Å)/Alq(500Å)/Mg:Ag(1000Å)/Ag(400Å)
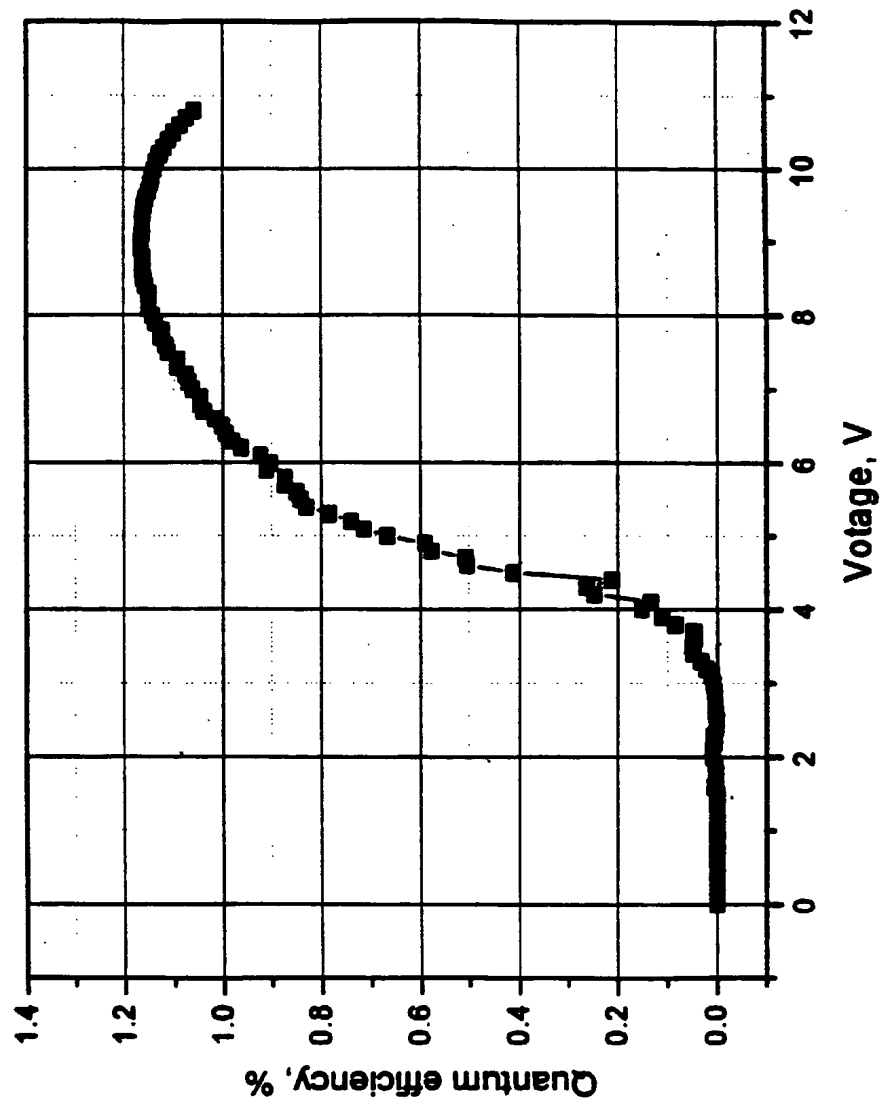
FIGURE 10

ITO/Co(ppz)₃(400Å)/Ga(pma)₃(100Å)/Alq(500Å)/Mg:Ag(1000Å)/Ag(400Å)
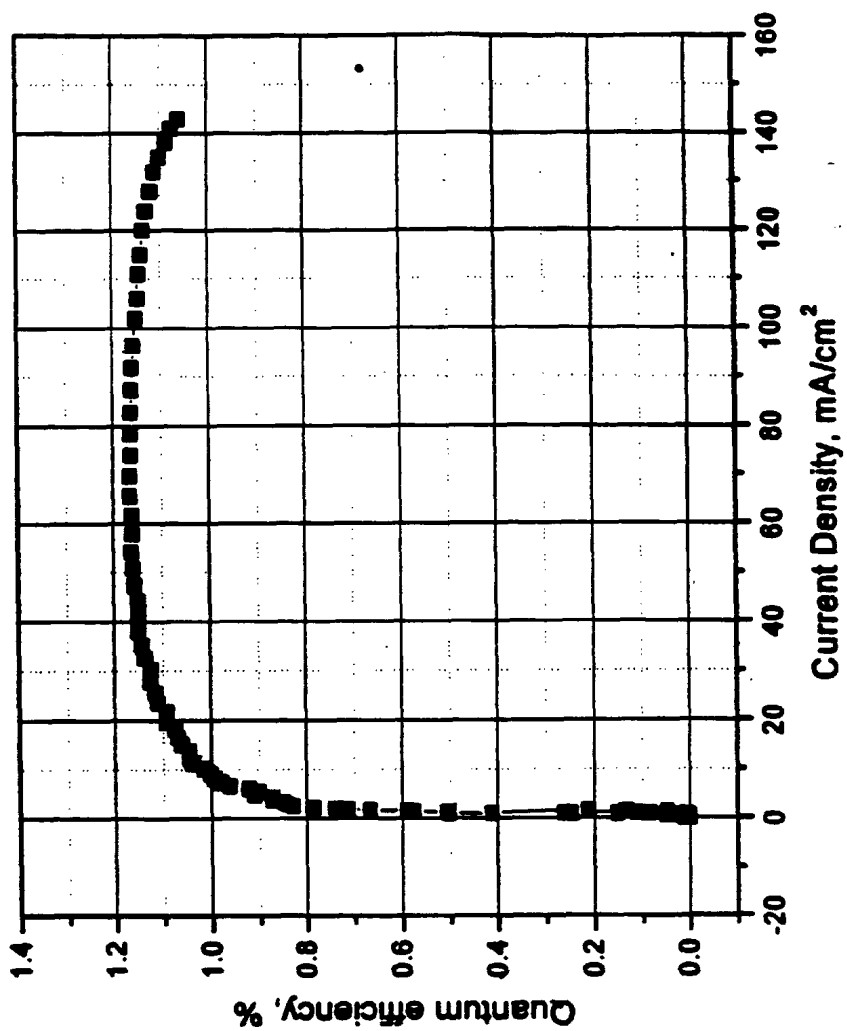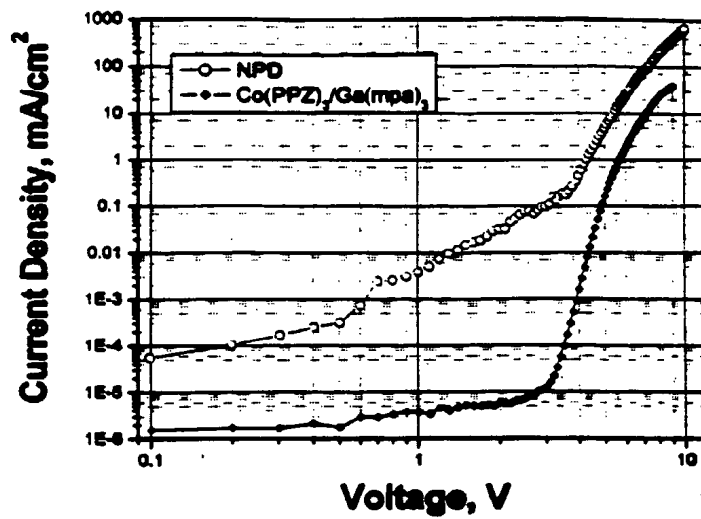
FIGURE 11A

I-V characteristics for NPD and Co(ppz)₃/Ga(mpa)₃ based OLEDs. Device structure:
ITO/HTL(500Å)/CBP:Irppy(6% 200Å)/BCP(150Å)/Alq₃(200Å)/LiF/Al

FIGURE 11B
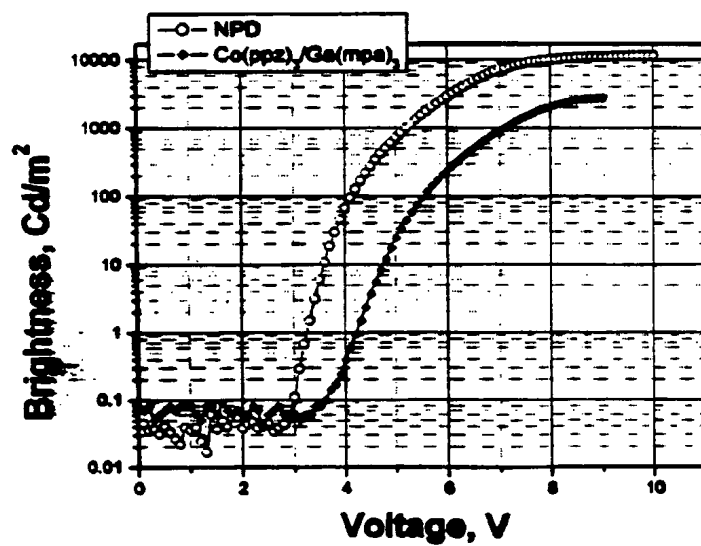
Brightness versus voltage for devices of Figure 7.

FIGURE 12A
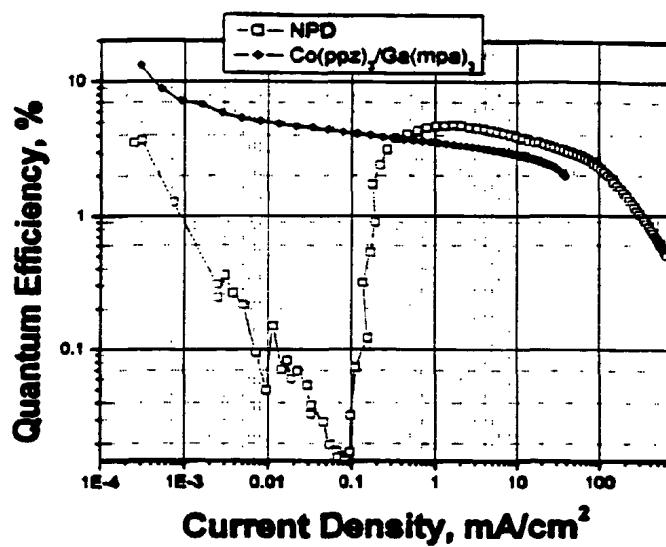
Quantum efficiency versus current density for the devices of Figure 7.

FIGURE 12B
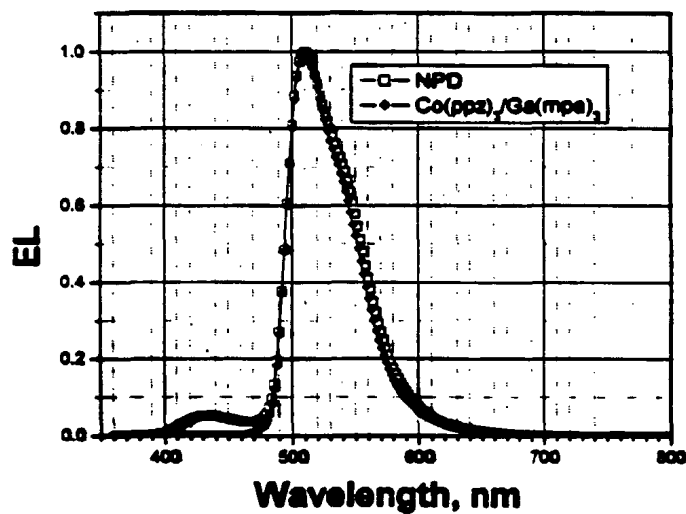
Emission spectra for the devices of Figure 7.

FIGURE 13

ITO/CoPhZ(400Å)/NPD(100Å)/Alq(500Å)/Mg:Ag(1000Å)/Ag(400Å)

13/27

FIGURE 14

14/27
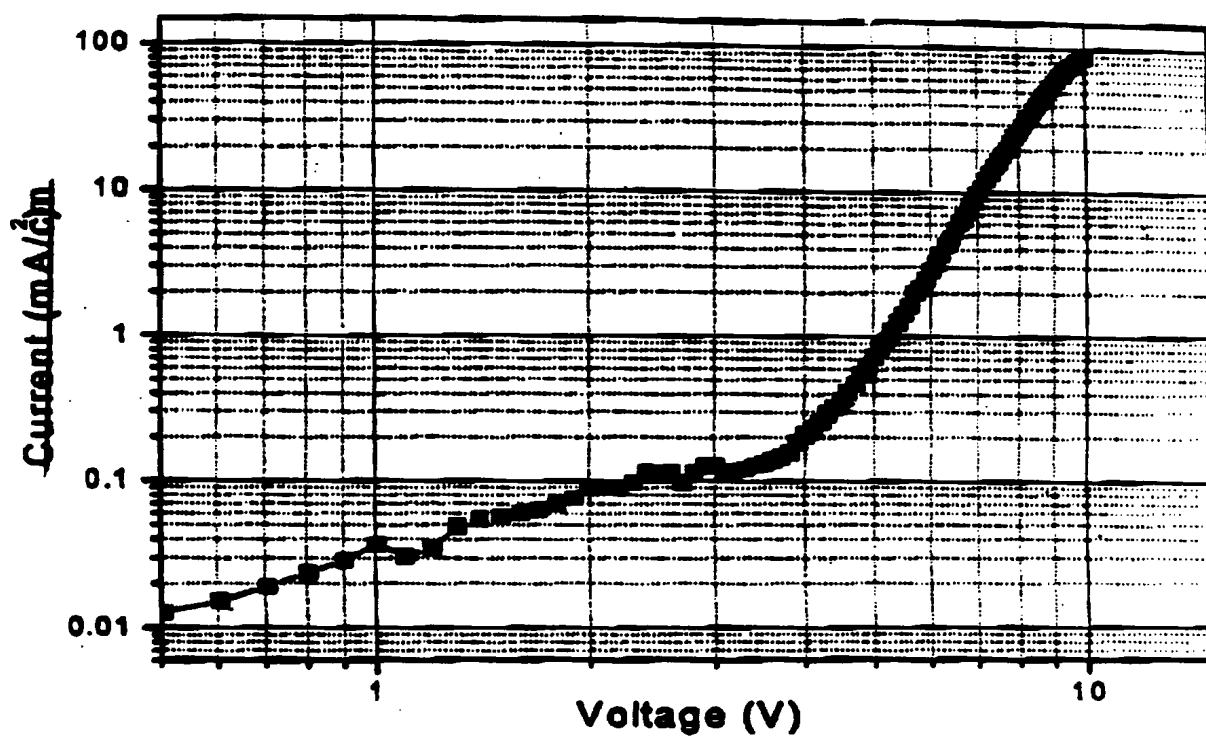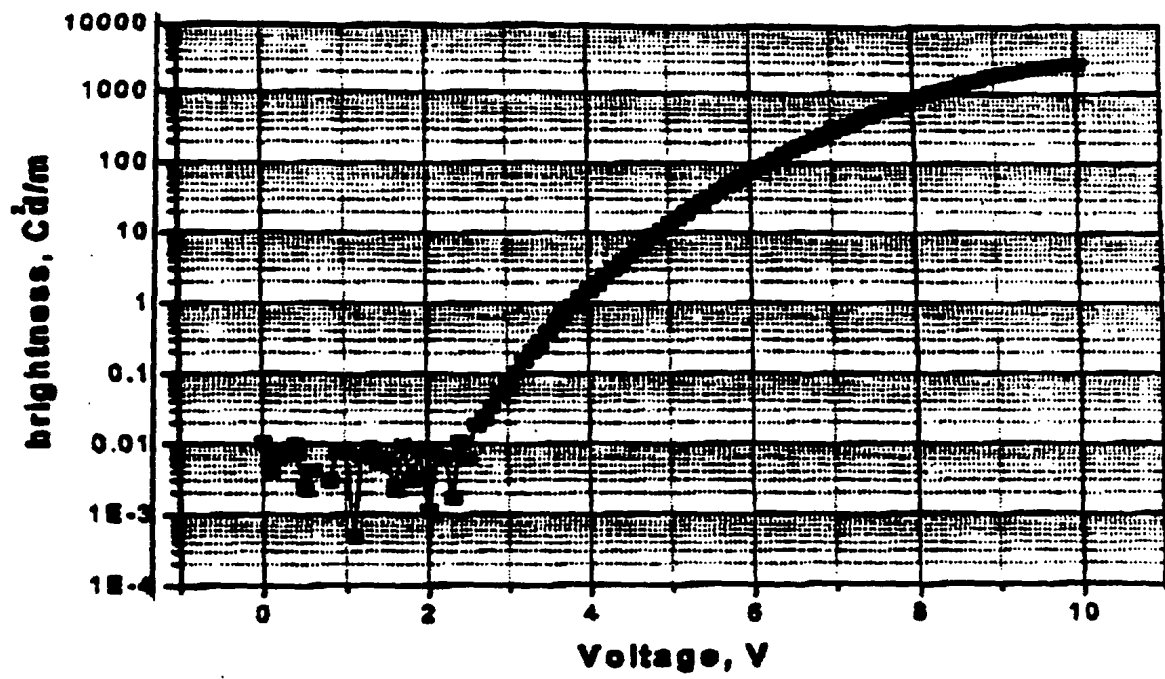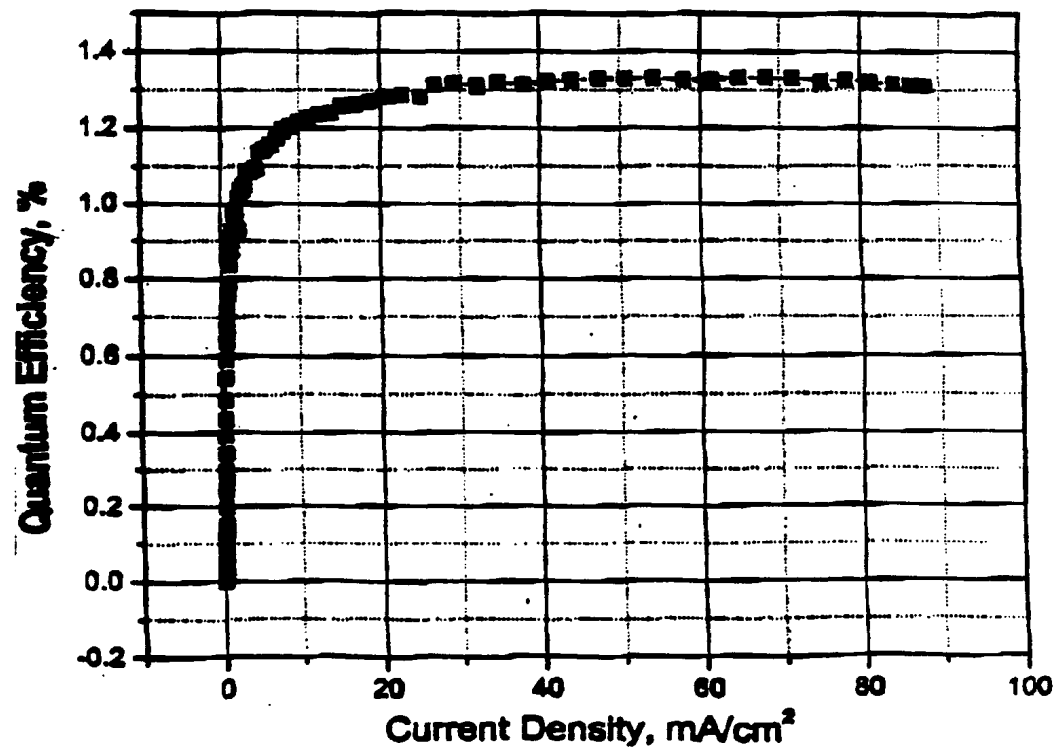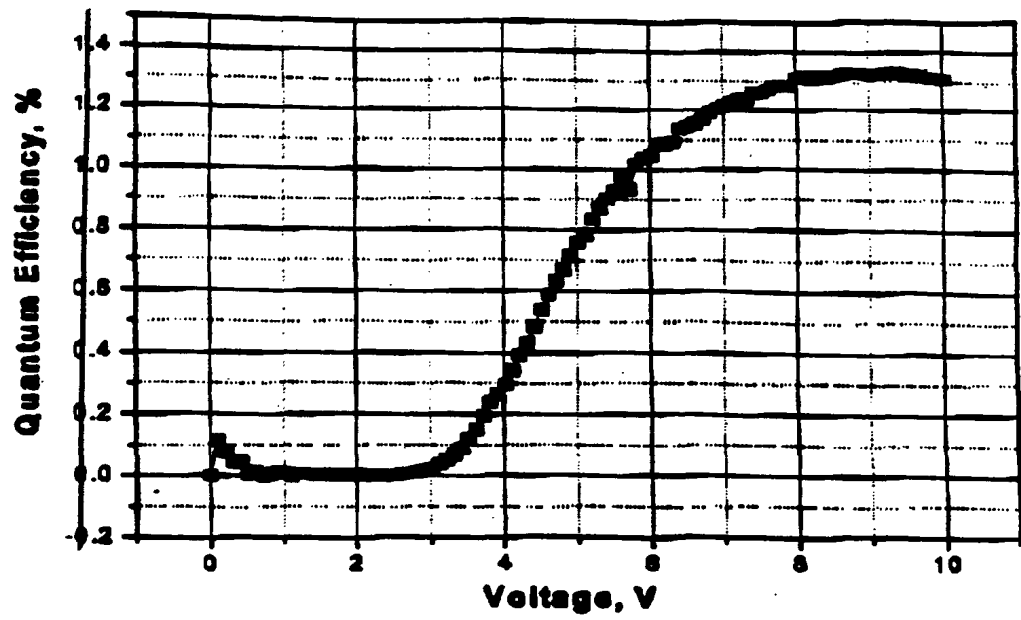
FIGURE 15

FIGURE 16

Conventional Hole-Transporting Materials used in OLEDs

a-NPD

TPTE

TPD

m-MTDATA
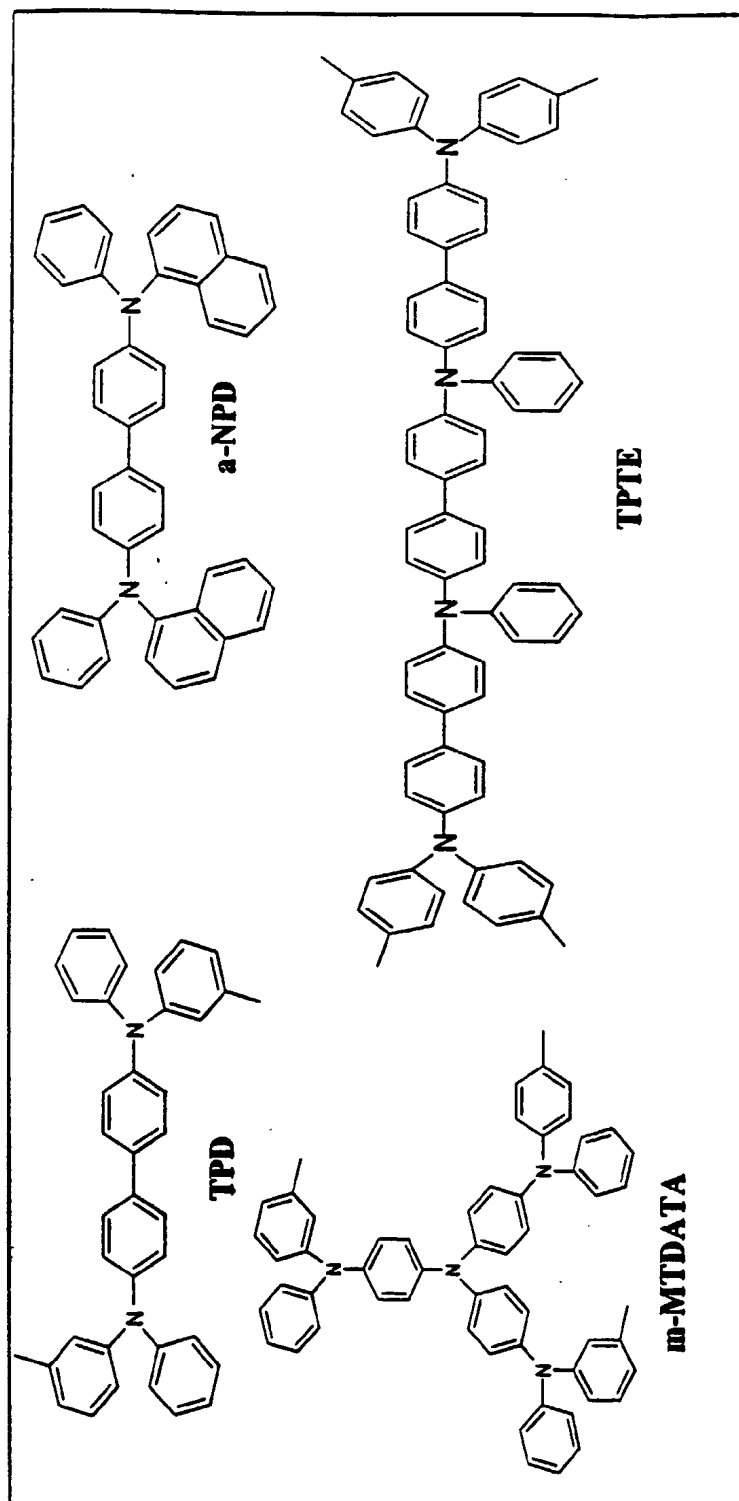
Triarylamine derivatives have proved to be excellent hole transporting materials for OLEDs. The hole mobilities in these materials are very high, due to the high degree of intermolecular π overlap and the planar nature of both the neutral and cationic forms of the molecules. The fact that both the neutral and cationic (hole) states for triarylamines leads to low reorganization energies and thus low barriers to electron transfer.

FIGURE 17

Organometallic Complexes may also be good candidates for charge transporting layers

Given the fact that metals have the ability to assume a variety of oxidation states, and the low kinetic barriers inherent in some organometallic self-exchange reactions.

Several efficient devices have been made incorporating the following organometallic complexes :

FIGURE 18
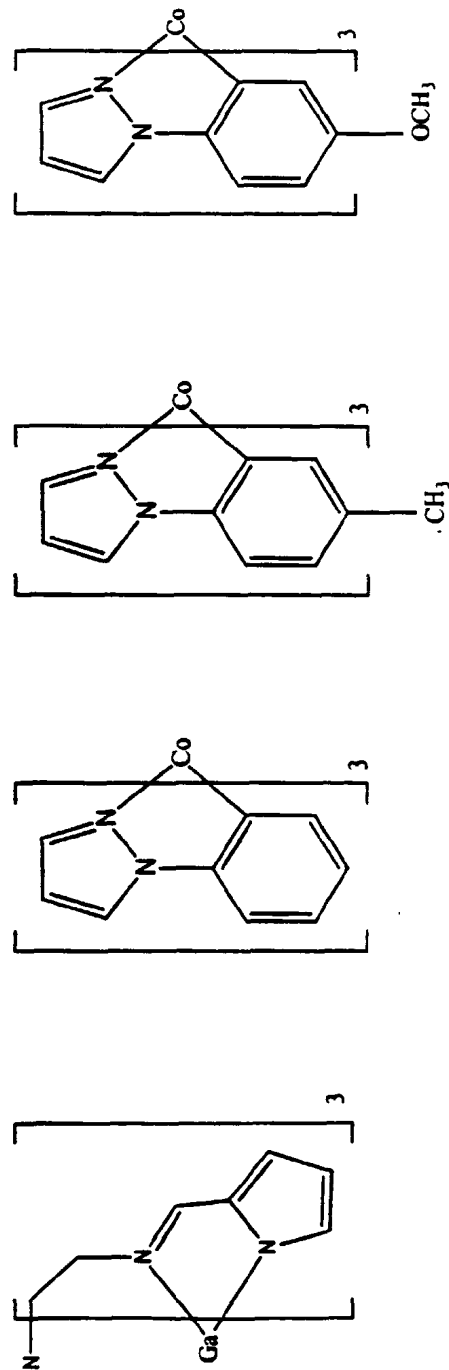
Electron Self-Exchange Reactions (carrier migration)

- $A^+ + A \rightarrow A + A^+$, self exchange leads to carrier migration

- At the instant of electron transfer, the nuclei remain stationary, with no energy change in the system.

- Before electron transfer from one center to another can take place, the system must adjust so that the energy of the system is unaltered during electron transfer.

- The amount of distortion required to reach a common state is inversely related to the rate of electron transfer.

Electronic configurations

$$\xrightarrow[+e]{-e}$$

e_g antibonding orbital

t_{2g} nonbonding orbital

Octahedral Co^{3+}

Octahedral Co^{4+}
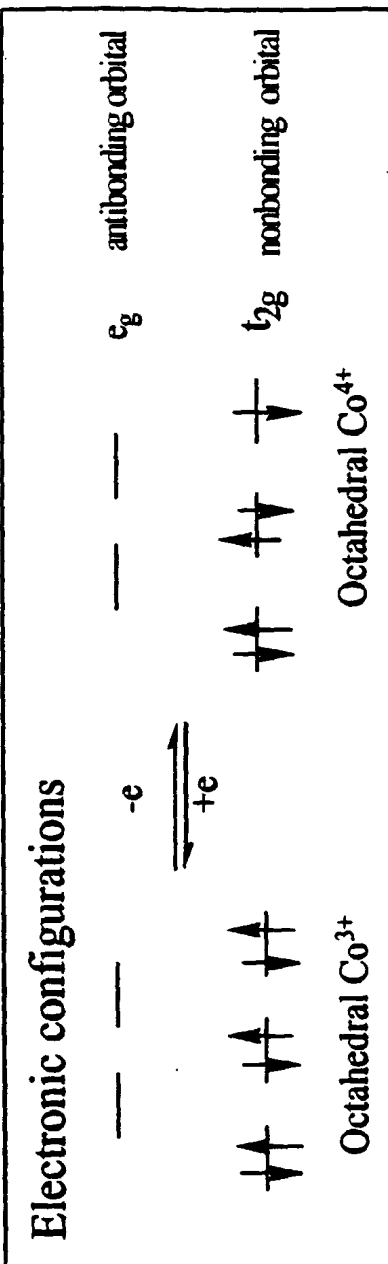
- Since t_{2g} is a nonbonding orbital, electrons into and out of this orbital involves small M-L changes.

- Since the two oxidation states have essentially the same structures, electron hopping between them may takes place with ease.

FIGURE 19

Synthesis of Cobalt (III) and Ga (III) Complexes

X= H, CH₃, OCH₃

(Step 1)

B(OH)₂ + H-N-N

Pyridine, Celite, CH₂Cl₂
r.t. 2 days

(Step 2)

+ CoBr₂

Grinard Reagent, dry THF
r.t., overnight

Co

+ Ga(NO₃)₃
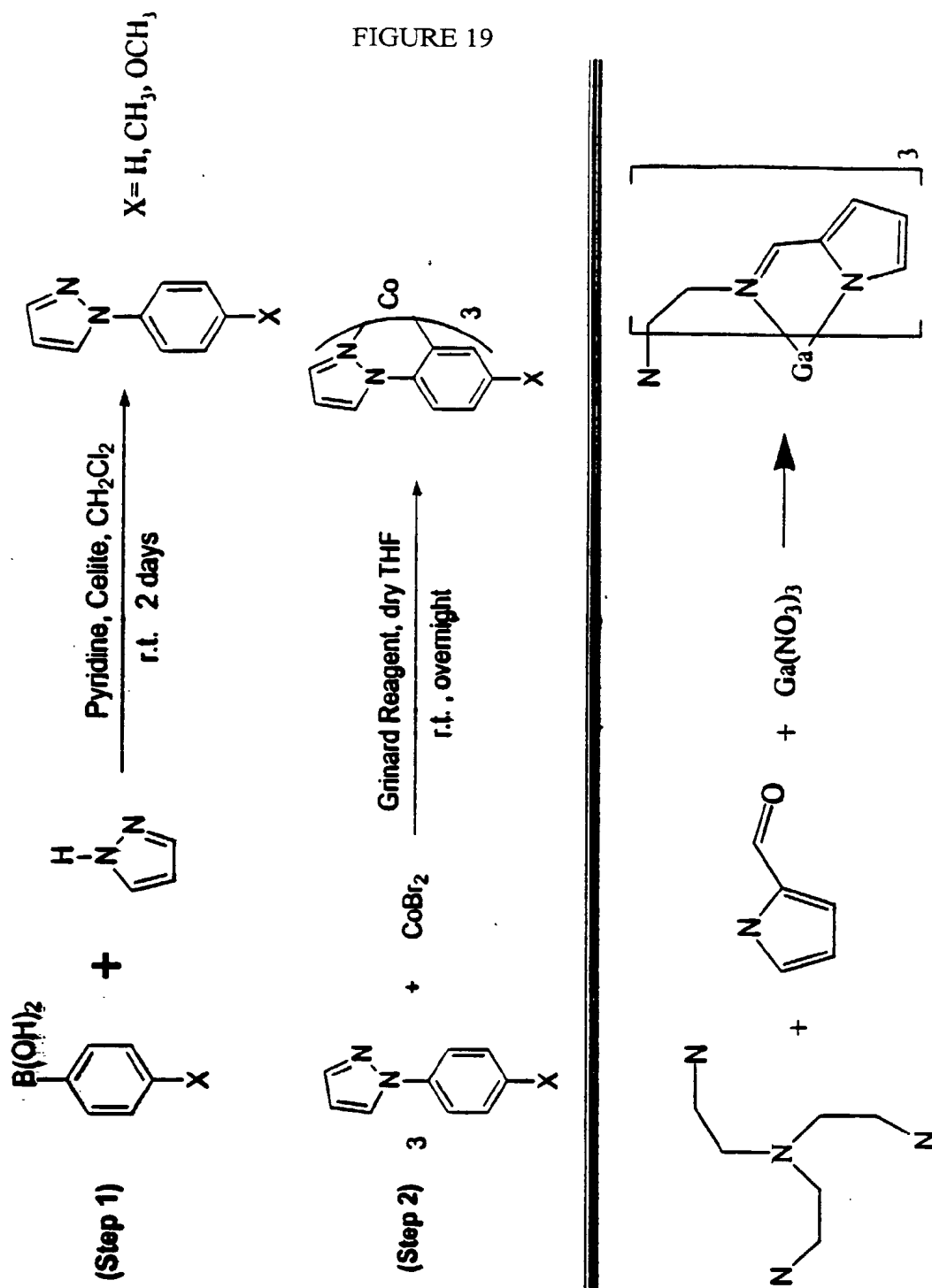
FIGURE 20

Absorption Spectrum

Absorption spectrum of PPZ
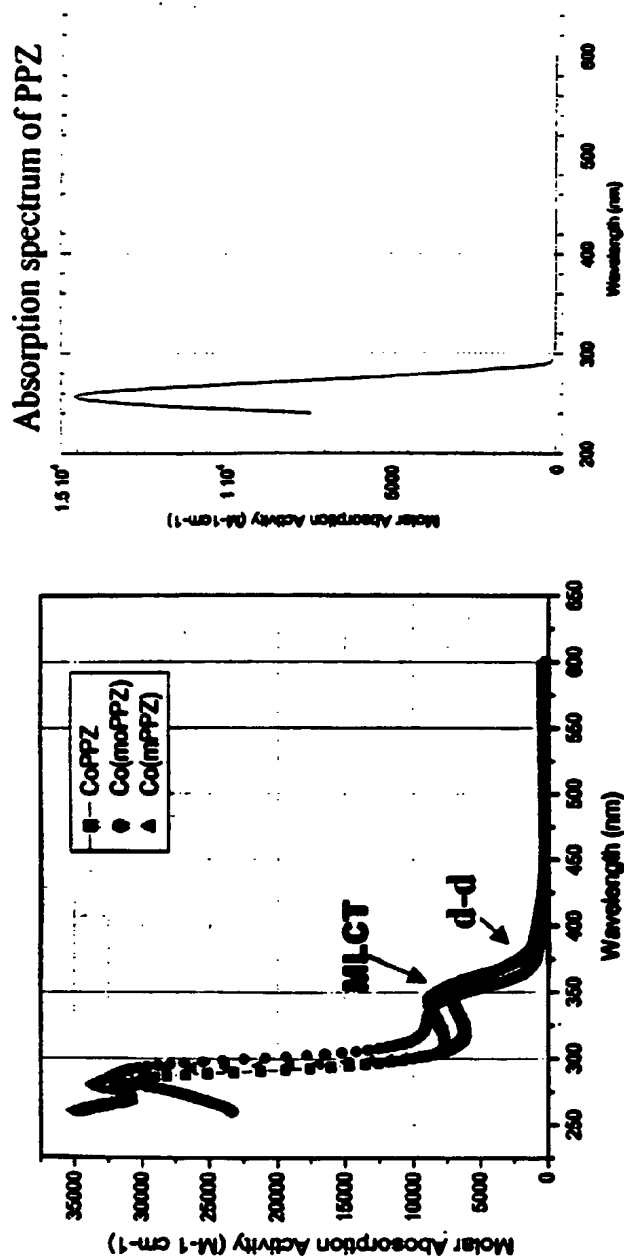
The intense peak below 300nm is assigned to the ligand-centered $\pi-\pi^*$ transition

The broad, structureless band around 340nm is assigned to a metal-to-ligand charge transfer (MLCT) transition

The broad shoulder in the low 400nm range corresponds to the *d-d* transition, characteristic of octahedral Co^{3+} complexes

FIGURE 21

Cyclic Voltammetry and Ultraviolet Photoemission Data

$Co(□)PPZ \longrightarrow Co(IV)PPZ^+$

The electron-rich phenylpyrazole ligand stabilizes the Co(□) species produced electrochemically.

Co(mPPZ)

Co(moPPZ)

CoPPZ

UPS Data (HOMO)
CoPPZ: 5.37eV
Co(mPPZ): 5.38eV
NPD: 5.51eV

FIGURE 22
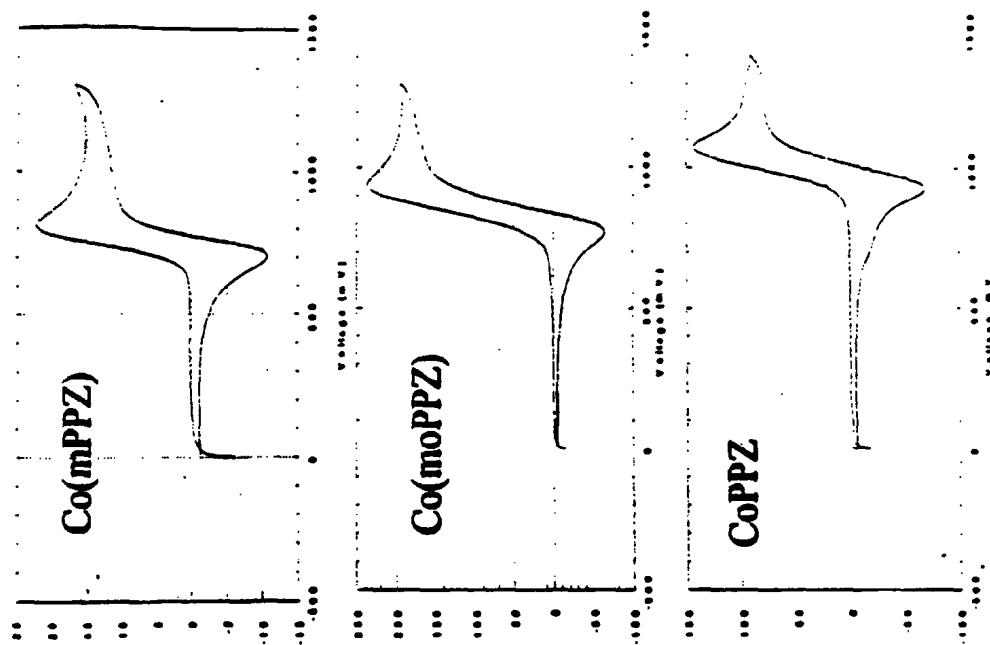
Device incorporating Co(xPPZ) as the Hole
Transporting Layer

Device Structure: ITO/Co(xPPZ)(250Å)/Alq(500Å)/Mg:Ag(1000Å)/Ag(400Å)

X = H, Black   X= OCH₃, Red   X=CH₃, Green
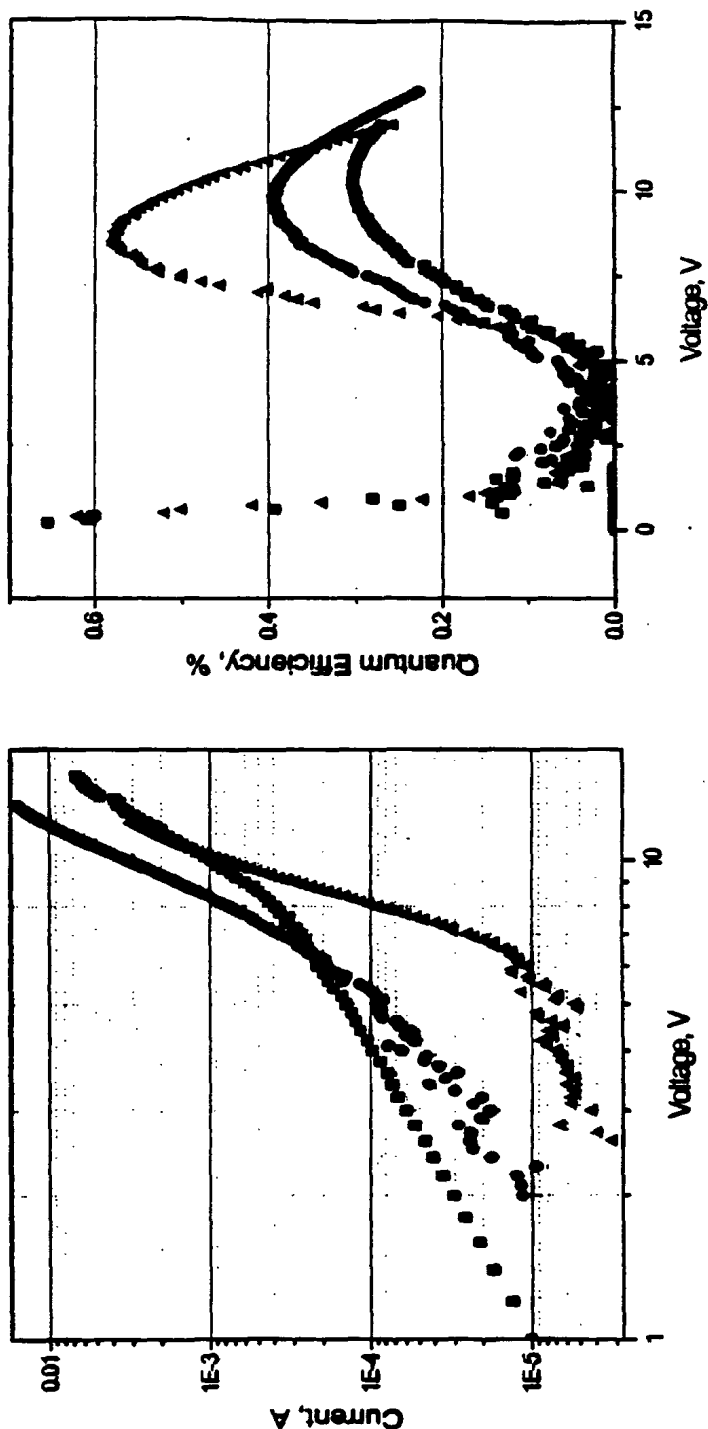
FIGURE 23

Introduction of a Thin NPD Layer as the Electron-Blocking Layer

ITO/CoPPZ(400Å)/NPD(100Å)/Alq(500Å)/Mg:Ag
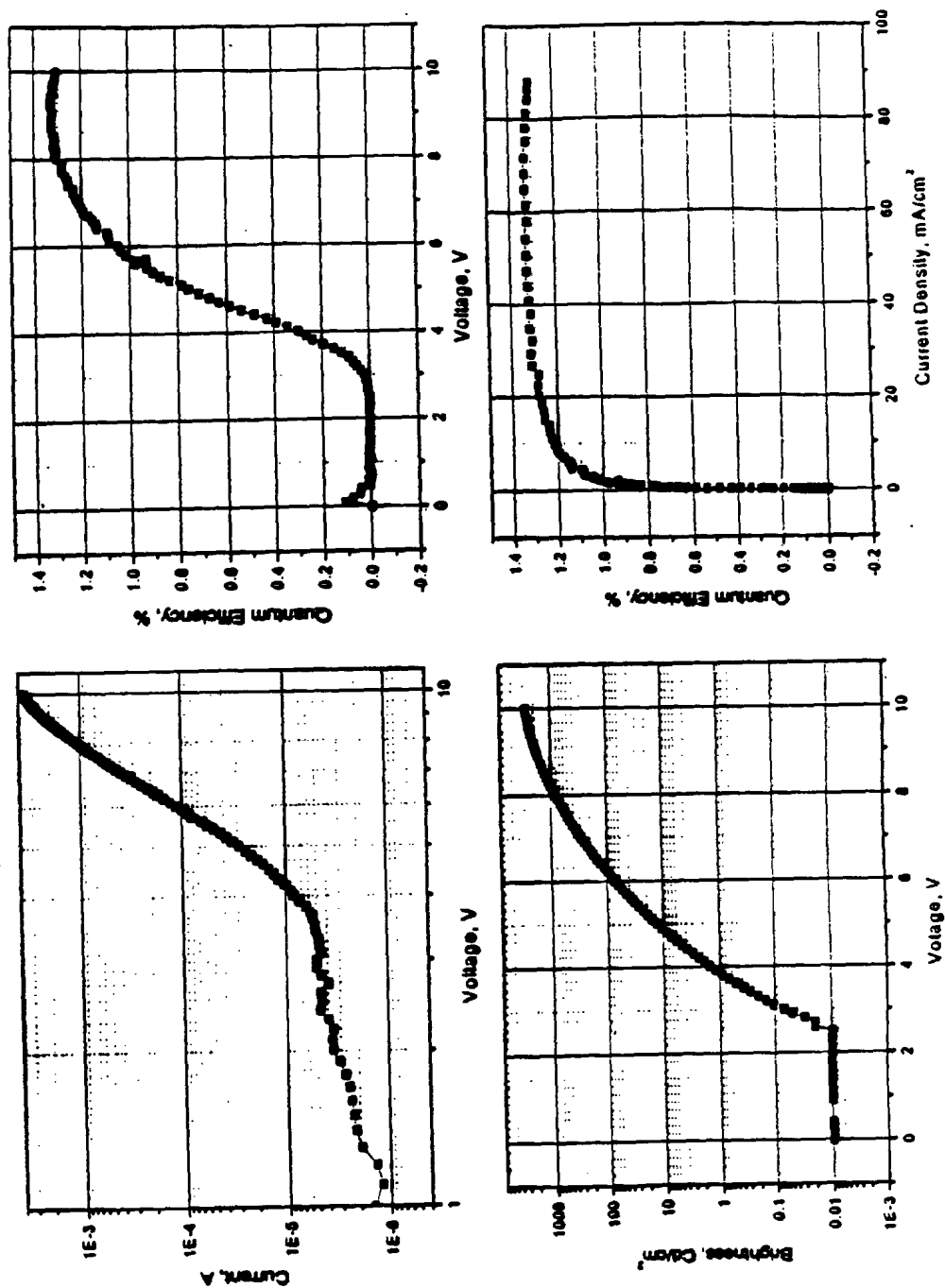
FIGURE 24

Photophysics of Ga(pma)₃

Ga(pma)₃
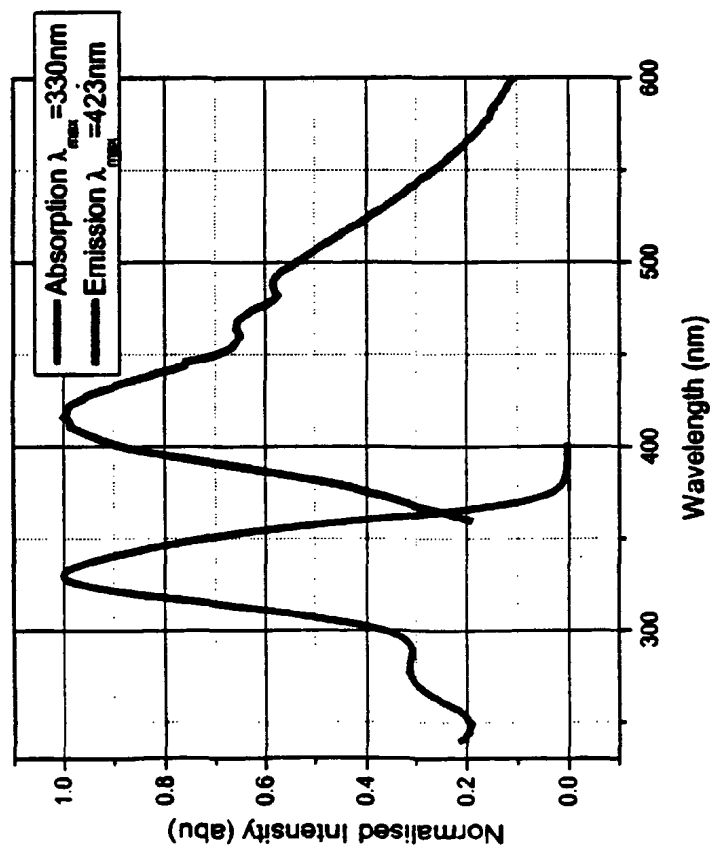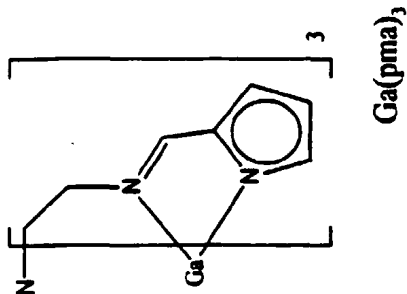
- A wide energy gap of about 3.4 eV can be obtained from the absorption and emission spectra
- Note that the hole transporting properties are at the tertiary N atom and not at the metal center

The HOMO energy level, 5.74 eV (calculated using ultraviolet emission spectroscopy), and LUMO energy level, 2.34eV, of Ga(pma)₃ makes this compound energetically suitable as a hole transporting/electron blocking layer between CoPPZ and Alq.

(No electrochemistry of Ga(mpa)₃ has been observed yet)

FIGURE 25

Efficient OLED with ONLY Metal Complexes(1)

ITO/Coppz(400Å)/GaPMAEA(100Å)/Alq(500Å)/Mg:Ag(1000Å)/Ag(400Å)

FIGURE 26

Efficient OLED with ONLY Metal Complexes(2)

ITO/Coppz(400Å)/GaPMAEA(100Å)/Alq(500Å)/Mg:Ag(1000Å)/Ag(400Å)
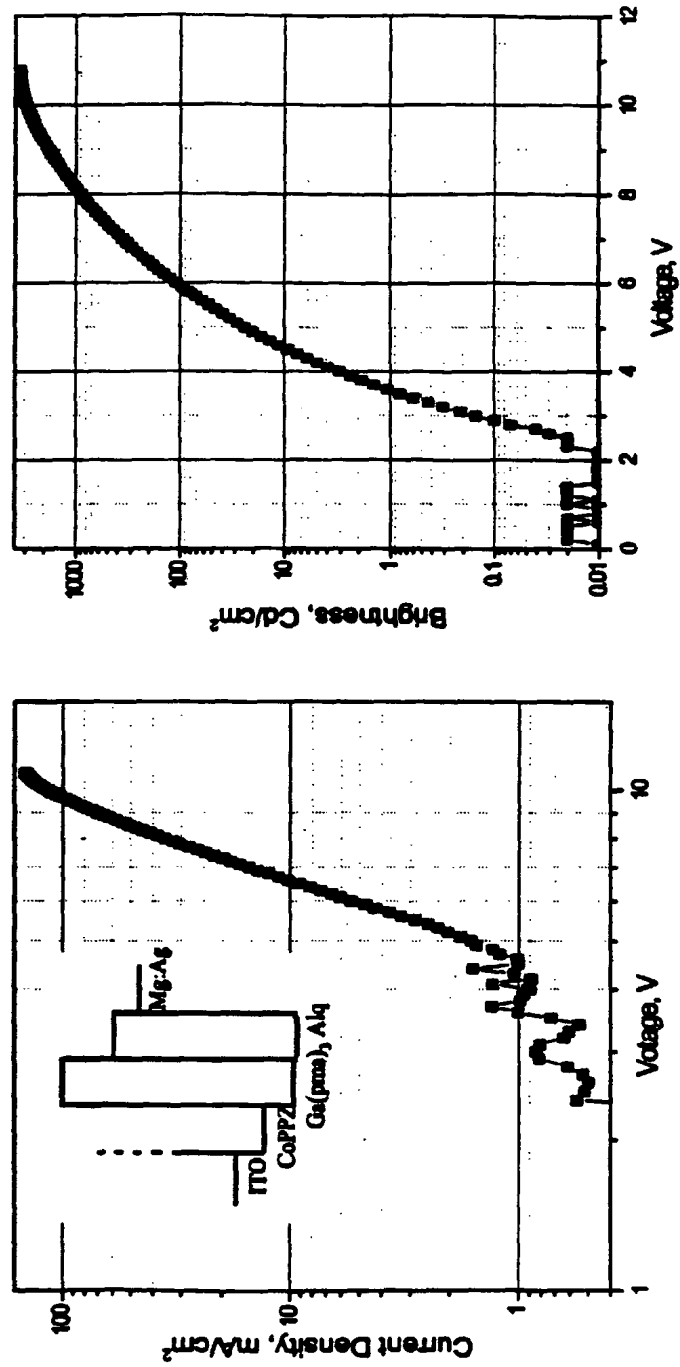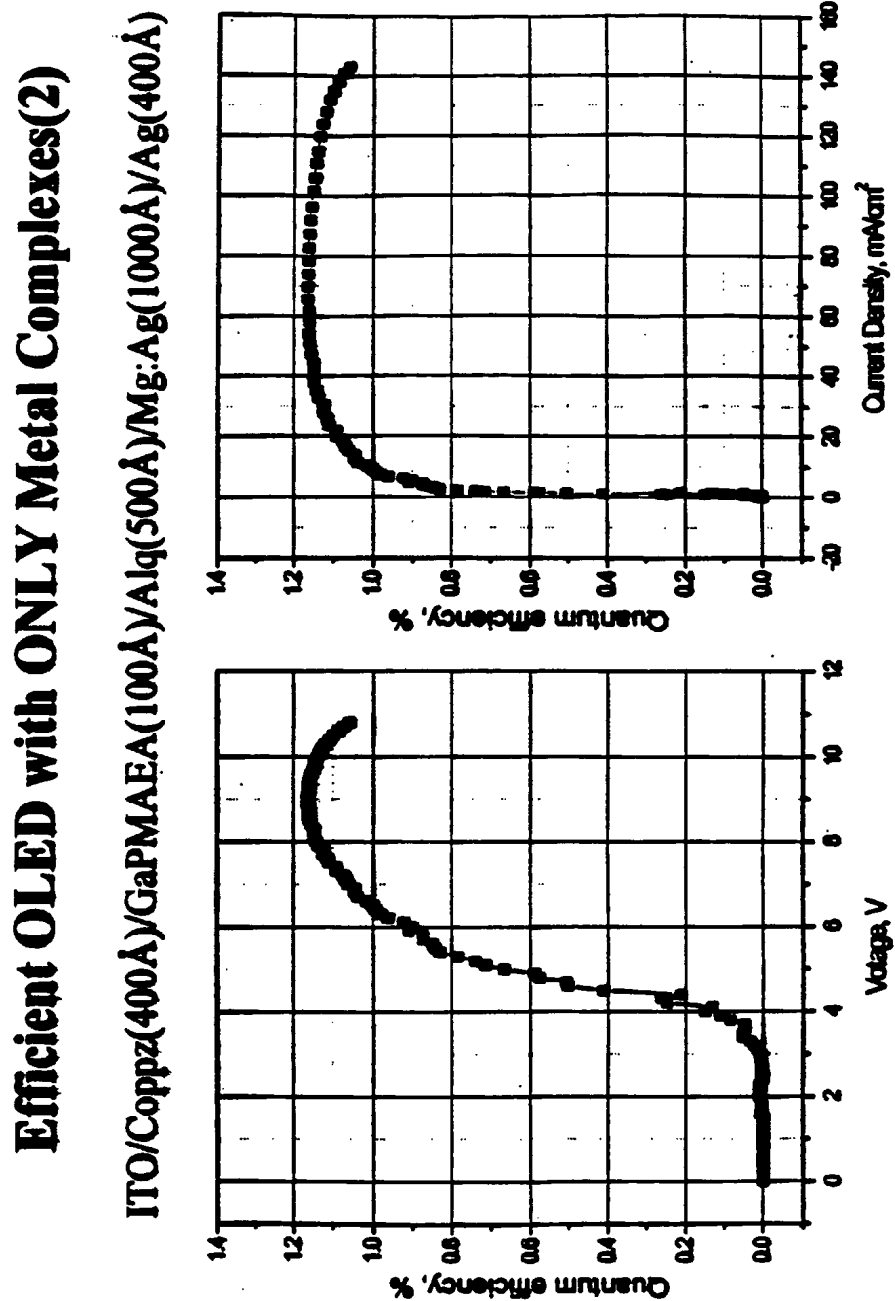
FIGURE 27

Introduction of CoPPZ/Gapma into the phosphorescence devices

HTL(500Å)/CBP:Irppy(6% 200Å)/BCP(150Å)/Alq₃(200Å)/LiF/Al
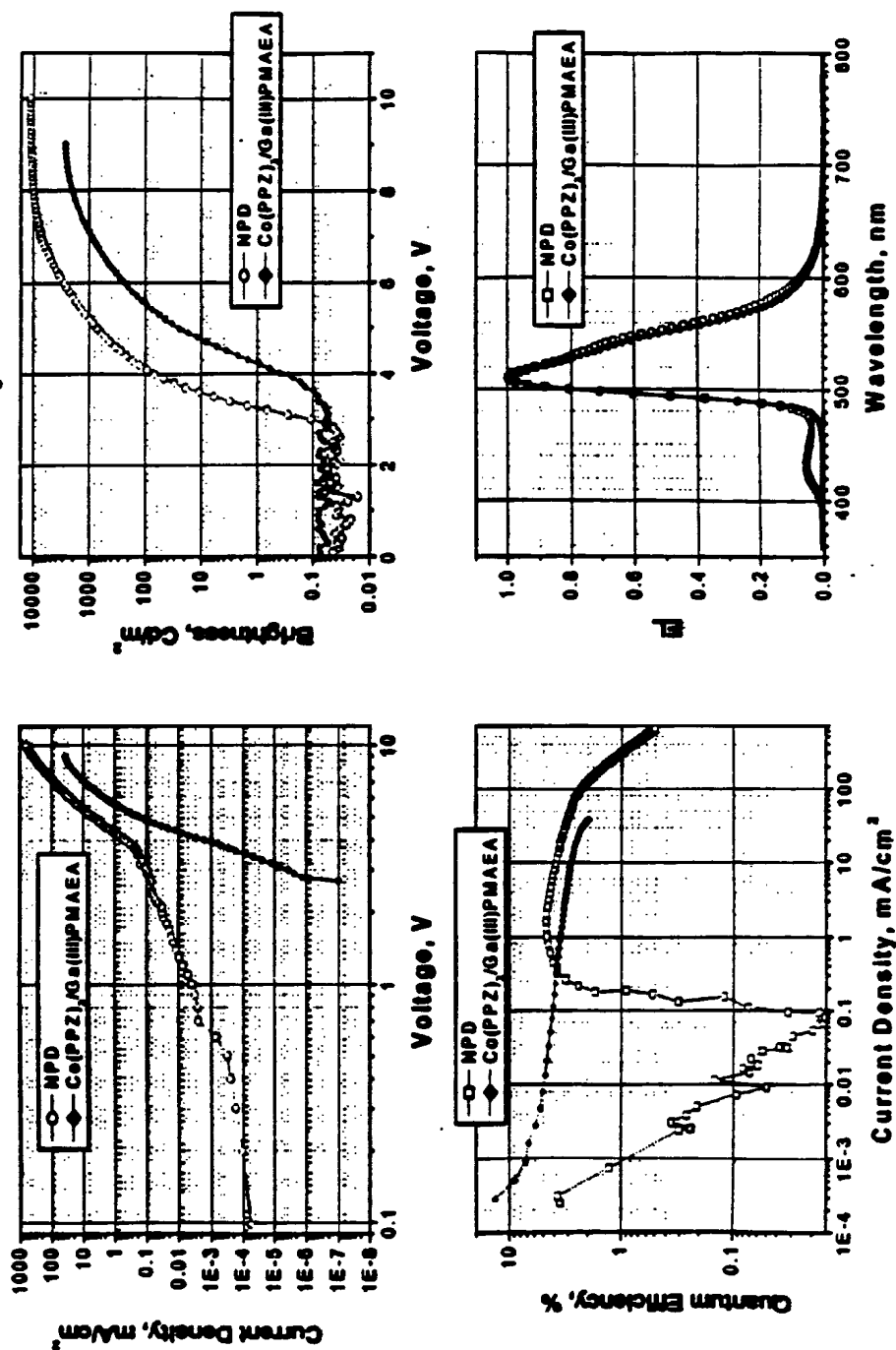
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7)   :   H05B 33/00
US CL   :   428/690, 917; 313/504

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 428/690, 917; 313/504

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P --- A, P	US 2002/0015860 A1 (MOTOMATSU et al) 07 February 2002 (07.02.2002), abstract, column 3, paragraph "0018", and entire patent.	1-8, 39-52, 59-68, 81, 82, 87, 88, 93 ----------- 9-38, 53-58, 69-80, 83-86, 89-92
A	US 6,010,796 A (KIJIMA) 04 January 2000 (04.01.2000), entire patent.	1-93
X --- A	US 5,693,962 A (SHI et al) 2 December 1997 (02.12.1997), column 6, lines 19-33.	1-3, 59-62, 82 ----------- 4-58, 63-81, 83-93

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier application or patent published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure. use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 September 2002 (30.09.2002)	16 DEC 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Cynthia Kelly Telephone No. (703)308-2351

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Continuation of B. FIELDS SEARCHED Item 3:
JPO, EPO, Derwent Abstracts, USPAT
search terms: exciton, hole transporting, electron blocking layer, organometallic

(51) International Patent Classification[7]: **H01B 1/00,** H05B 33/00

(21) International Application Number: PCT/US02/27202

(22) International Filing Date: 27 August 2002 (27.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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(71) Applicant *(for all designated States except US)*: **THE UNIVERSITY OF SOUTHERN CALIFORNIA** [US/US]; 3716 South Hope Street, Suite 313, Los Angeles, CA 90007 (US).

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(54) **Title:** DOPED ORGANIC CARRIER TRANSPORT MATERIALS

(57) **Abstract:** The present invention provides for organometallic and organic dopants suitable for use in organic carrier transporting materials. Also provided are organic light emitting devices containing doped organic carrier transporting materials.

DOPED ORGANIC CARRIER TRANSPORT MATERIALS

FIELD OF THE INVENTION

[0001]   The present invention pertains to the field of doped organic charge transporting materials and organic light emitting devices containing such materials.

BACKGROUND OF THE INVENTION

[0002]   Of the known electronic display technologies, organic light emitting devices (OLEDs) are of considerable interest for their potential role in the development of full color, flat-panel display systems.   OLEDs are comprised of several organic layers in which at least one of the layers can be made to electroluminesce by applying a voltage across the device (see, e.g., Tang, *et al.*, *Appl. Phys. Lett.* **1987**, *51*, 913 and Burroughes, *et al.*, *Nature*, **1990**, *347*, 359).   When a voltage is applied across a device, holes and electrons migrate toward their respective oppositely charged electrodes.   Recombination of the hole and electron is accompanied by radiative emission, thereby producing electroluminescence.

[0003]   Movement of charge across an OLED is typically facilitated by inclusion of organic carrier transport layers.   Organic materials used in this capacity generally are characterized as having high charge mobility and a low barrier to charge injection. Despite these favorable charge transporting characteristics, conductivity remains relatively low, especially in comparison to doped inorganic semiconductor devices. Consequently, OLEDs often have undesirable high operating voltages.

[0004]   In contrast with doped inorganic semiconductor light emitting diodes or lasers, nominally undoped OLEDs have low intrinsic carrier concentrations. Intentional doping of the organic charge transporting layer has been studied as a possible means for remedying this deficiency and improving conductivity and power efficiency. p-Type doping of organic hole transporting materials with the organic compound tetrafluoro-tetracyano-quinodimethane (F_4-TCNQ) has been reported in Blochwitz, *et al.*, *Appl. Phys. Lett.*, **1998**, *73*, 729; Pfeiffer, *et al.*, *Appl. Phys. Lett.*, **1998**, *73*, 3202; Zhou, *et al.*, *Appl. Phys. Lett.*, **2001**, *78*, 410; and Blochwitz, *et al.*, *Organic Electronics*, **2001**, *2*, 97. Similarly, n-type doping is the subject of Nollau, *et al.*, *J. Appl. Phys.*, **2000**, *87*, 4340 which reports doping of naphthalenetetracarboxylic dianhydride (NTCDA) with bis(ethylenedithio)-tetrathiafulvalene (BEDT-TTF). OLEDs containing both p- and n-type doped hole and electron transporting layers, respectively, are reported in Huang, *et al.*, *Appl. Phys. Lett.*, **2002**, *80*, 139. Doped polymeric hole transporting layers are reported in Yamamori, *et al.*, *Appl. Phys. Lett.* **1998**, *72*, 2147; Yamamori, *et al.*, *J. Appl. Phys.*, **1999**, *86*, 4369; and JP 11283750. Electron transporting layers doped with metals are reported in Kido, *et al.*, *Appl. Phys. Lett.*, **1998**, *73*, 2866; WO 01/41513; EP 1089361; and EP 1011155.

[0005]   Currently, few compounds have been identified as suitable for enhancing conductivity in OLEDs. Known dopants are typically useful only in combination with a narrow range of organic charge transporting materials. In this regard, new dopants are needed, including more versatile dopants that can be readily adjusted or "tuned" to energetically fit with any given charge transporting material. Identification of new dopants can result in improved OLEDs having higher power efficiency, lower driving voltages, more efficient charge injection, and improved conductivity. The compositions, methods, and devices described herein help fulfill these and other needs.

SUMMARY OF THE INVENTION

[0006]   The present invention provides charge transporting materials comprising an organic matrix and an organometallic dopant, where the charge transporting material has a higher conductivity than undoped organic matrix.

[0007]   The present invention further provides for electron transporting materials comprising an organic matrix and an organometallic dopant, where the dopant is capable

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of transferring electrons to the organic matrix, and where the electron transporting material has a higher conductivity than undoped organic matrix.

[0008]   In other embodiments, the present invention provides hole transporting materials comprising an organic matrix and an organometallic dopant, where the dopant is capable of transferring holes to the organic matrix, and where the hole transporting material has higher conductivity than undoped organic matrix.

[0009]   The present invention also provides methods for selecting an organometallic dopant for increasing conductivity of an organic matrix of an electron transporting material, comprising determining the ionization potential of the dopant determining the LUMO energy level of the organic matrix; and selecting the dopant if the ionization potential is lower than the LUMO energy level, or if the ionization potential is within about 0 to about 0.5 eV of the LUMO energy level.

[0010]   Simlarly, the present invention also provides methods for selecting an organometallic dopant for increasing conductivity of an organic matrix of a hole transporting material, comprising: determining the ionization potential of the organic matrix; determining the LUMO energy level of the dopant; and selecting the dopant if the ionization potential is lower than the LUMO energy level, or if the ionization potential is within about 0 to about 0.5 eV of the LUMO energy level.

[0011]   Further provided by the present invention are charge transporting materials comprising an organic matrix and a dopant, where the dopant is an organometallic compound comprising at least one cyclopentadienyl ligand optionally substituted by one or more substituents selected from H, an electron withdrawing substituent, or an electron donating substituent.

[0012]   According to other embodiments, the present invention provides charge transporting materials comprising an organic matrix and a dopant, where the dopant is an organometallic compound comprising at least one arene ligand optionally substituted by one or more substituents selected from H, an electron withdrawing substituent, or an electron donating substituent.

[0013]   In yet other embodiments, the present invention provides charge transporting materials comprising an organic matrix and a dopant, where the dopant is an organometallic compound comprising at least one carborane ligand optionally substituted

by one or more substituents selected from H, an electron withdrawing substituent, or an electron donating substituent.

[0014]   The present invention further provides charge transporting materials comprising an organic matrix and a dopant, where the dopant is a metallocene having the formula $M(L^1)(L^2)$, wherein L^1 has the formula:
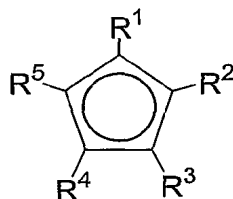
and L^2 has the formula:
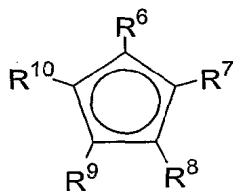
wherein:

each R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is, independently, H, an electron withdrawing substituent, or an electron donating substituent; and

M is a metal atom.

[0015]   The present invention further provides charge transporting materials comprising an organic matrix and a dopant, where the dopant has the formula $M(Ar)_4$, wherein M is a metal atom, Ar is an aryl group substituted by one or more R^{11}, wherein each R^{11} is, independently, H, an electron withdrawing substituent, or an electron donating substituent.

[0016]   Further provided by the present invention are charge transporting materials comprising an organic matrix and a dopant, where the dopant has the formula:
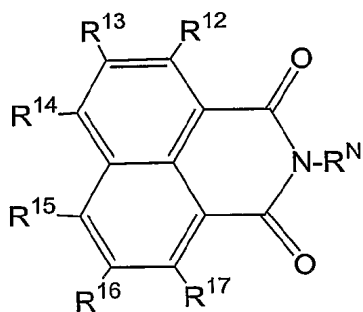
wherein each R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^N is, independently, H, an electron withdrawing substituent, or an electron donating substituent.

[0017]   The present invention further provides charge transporting materials comprising an organic matrix and a dopant, where the dopant is incapable of transferring charge to the organic matrix except when the dopant is optically excited.

[0018]   Also provided by the present invention are organic light emitting devices comprising any charge transporting materials described above.

[0019]   In yet further embodiments, the present invention provides methods for increasing the power efficiency of an organic light emitting device comprising incorporating in the device any charge transporting material described above.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0020]   The present invention provides for, *inter alia*, charge (carrier) transporting materials containing an organic matrix (or host) material into which an organic or organometallic compound is doped. Doping can effectively increase the number of carriers in the charge transporting material, leading to improved or higher conductivity relative to undoped organic matrix. Ultimately, the doped materials can help increase power efficiencies of OLEDs and improve operation of other electronic devices by providing a route for lower resistance and, hence, lower voltage operation.

[0021]   Organic matrix material typically contains one or more substances that facilitate either electron or hole transport. Materials suitable as organic matrix for use in the doped hole transporting materials of the present invention include any material that is recognized by one skilled in the art to function as a charge transporting material. Such materials typically show high charge mobility, having low reorganizational barriers to redox events. Organic matrix can include organic compounds or compounds having an

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organic component, such as, for example, metal complexes having one or more organic ligands. Organic matrix can also include polymers, such as those derived from molecular starting materials.

[0022]   As with any chemical substance, organic matrix that is considered "pure" or "undoped" can still contain small amounts of impurities. Unlike for an impurity, however, a dopant is intentionally added to a substance, usually to achieve a certain property or result. Accordingly, as used throughout, the phrase "undoped organic matrix" refers to matrix material in that not intentionally doped.

[0023]   Organic matrix suitable for transporting holes can be, or contain, compounds that are readily oxidized and show little or no structural change upon oxidation. Suitable materials for organic matrix of hole transporting material can include, for example, triarylamines, phthalocyanines, metal phthalocyanines, porphryins, metal porphyrins, indolocarbazoles, metal complexes, iminostilbene containing compounds, or carbazole containing compounds. Triaryl amines such as N,N'-diphenyl-N,N'-bis(3-methylphenyl)1-1'biphenyl-4,4'diamine (TPD), 4,4'-bis[N-(1-naphthyl)-N-phenyl-amino]biphenyl (α-NPD), 4,4'-bis[N-(2-naphthyl)-N-phenyl-amino]biphenyl (β-NPD), and the like, are some examples of compounds suitable as organic matrix in hole transporting materials of the present invention. In some embodiments, metal complexes may also be used as organic matrix. Some suitable metal complexes are described, for example, in U.S. Application Ser. No. 60/283,814, filed April 13, 2001, which is incorporated herein by reference in its entirety. Further, organic matrix suitable for transporting holes can include polymers such as polyvinylcarbazoles, polyphenylenevinylenes, triarylamine pendent polymers, and others.

[0024]   Similarly, compounds suitable as organic matrix for transporting electrons are numerous and typically include compounds that are readily reduced and show little or no structural change upon reduction. Accordingly, suitable electron transporting materials can include, for example, unsaturated hydrocarbons (carbocyclic and open chain), unsaturated N- and O-containing heterocycles, and metal complexes. Representative unsaturated hydrocarbons include cyclooctatetraenes, cyclopentadienes, siloles, and the like. An example of a cyclooctatetraene is octaphenylcyclooctatetraene. Representative unsaturated N- and O-containing heterocycles include phenanthrolines, carbazoles, oxidiazoles, triazoles, triazines, imidazoles, benzimidazoles, and the like. An

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example of a phenanthroline is bathocuprione. An example of a carbazole is 4,4'-dicarbazolyl-biphenyl.   An example of a triazole is 3-phenyl-4-1-naphthyl-5-phenyl-1,2,4-triazole. An example of an oxidiazole is 3-(p-tertiary butyl-phenyl)-4-(p-biphenyl)-1,2,-oxidiazole. Other unsaturated heterocycles are also suitable, such as, for example, thiophene and oligothiophene. Some suitable metal complexes can include, for example, metal quinolates such as aluminum tris(8-hydroxyquinolate) (Alq$_3$), zirconium tetra(8-hydroxyquinoline), hafnium tetra(8-hydroxyquinoline), and the like.   Suitable organic matrix materials also include organometallic complexes in general, including tetraaryl metal complexes. Further, organic matrix suitable for transporting electrons can include polymers such as cyano substituted polyphenylenevinylenes and oxidiazole- and triazole-containing polymers.

[0025]   The organic matrix can be doped with a compound that increases conductivity of undoped organic matrix. While not wishing to be bound by theory, it is believed that such dopants function in a manner analogous to that of n- and p-type dopants of inorganic semiconductors (e.g., Si). That is to say, the dopant effectively transfers electrons (or holes) to the the matrix material, thereby increasing the overall charge density of the conducting matrix. Accordingly, the relative energetics of the dopant and matrix govern electron transfer from one to the other and, hence, the type of doping that can be achieved. For n-type doping, dopant acts as an electron donor by transferring electrons to the matrix (i.e., reducing the matrix). Conversely, in p-type doping, electrons are transferred from matrix to dopant (i.e., holes are transferred from dopant to matrix; the dopant effectively oxidizes the matrix). The material donating electrons can be considered a donor and the material receiving electrons can be considered an acceptor.

[0026]   Whether a donor will or will not transfer electrons to an acceptor, as well as the degree of transfer, can be determined by comparison of the energy levels of the HOMO and LUMO of the donor and acceptor, respectively. For example, if the energy of the donor HOMO is above that of the acceptor's LUMO, electron transfer from donor to acceptor can occur. Electron transfer can also occur when the HOMO energy level of the donor is below that of the LUMO energy level of the acceptor, so long as the difference in energy is sufficiently small so as to allow some thermal population of the higher energy orbital.

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[0027]   The HOMO energy level is related to, and can be derived from, ionization potential. For example, higher HOMO energy levels (shallower) correspond to a lower ionization potential because it would take less energy to remove an electron from the molecule. Ionization potential can be measured by techniques well known in the art such as, for example, UPS. Thus, in some embodiments, ionization potential can be used as an estimate of HOMO energy. Accordingly, degree of electron transfer from donor to acceptor, can be determined by comparison of ionization potential of the donor with the LUMO energy level of the acceptor. For example, if the ionization potential of the donor is less than the energy level of the acceptor's LUMO, electron transfer from donor to acceptor can occur. Electron transfer can also occur when the ionization potential of the donor is greater than the LUMO energy level of the acceptor, so long as the difference in energy is sufficiently small so as to allow some thermal population of the higher energy orbital.

[0028]   In this respect, for electron transporting materials, dopant can be selected such that electron transfer can occur from dopant to matrix. Thus, according to some embodiments, the energy level of the HOMO of the dopant can be above that of the energy level of the matrix LUMO. For example, the HOMO of the dopant can be about 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1 eV, or greater in energy than the LUMO energy level of the matrix. Accordingly, dopant can have an ionization potential lower than the LUMO energy level of the organic matrix. Ionization potential can be lower by any amount of energy, such as, for example, about 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1 eV, or more.

[0029]   According to some electron transporting materials of the present invention, the energy level of the HOMO of the dopant can be substantially the same as, or near the energy level of the LUMO of the matrix. In this regard, the difference between the respective HOMO and LUMO energy levels can range, for example, from about 0 to about 0.5 eV, about 0 to about 0.3 eV, about 0 to about 0.2 eV, about 0 to about 0.1 eV, or and even smaller range. In other embodiments, ionization potential of the dopant can be close to or near the energy level of the LUMO of the matrix. For example, the ionization potential of the dopant can be within about 0 to about 0.5 eV, about 0 to about 0.3 eV, about 0 to about 0.2 eV, or about 0 to about 0.1 eV of the LUMO energy level of the matrix.

[0030]   Conversely, for hole transporting materials, dopant can be selected such that electron transfer occurs from matrix to dopant (i.e., holes are transferred from dopant to matrix). Thus, according to some embodiments, the energy level of the HOMO of the matrix can be above that of the energy level of the LUMO of the dopant. For example, the HOMO energy level of the matrix can be greater by about 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, or 1 eV, or more, than the LUMO energy level of the dopant. Similarly, according to some hole transporting materials of the present invention, matrix can have an ionization potential less than the LUMO energy level of the organic matrix. In this regard, ionization potential can be lower by any amount of energy, such as, for example, about 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 1 eV, or more.

[0031]   In other embodiments, the energy level of the HOMO of the matrix can be substantially the same as, or near the energy level of the LUMO of the dopant. In this regard, the difference between the respective HOMO and LUMO energy levels can range, for example, from about 0 to about 0.5 eV, about 0 to about 0.3 eV, about 0 to about 0.2 eV, about 0 to about 0.1 eV, or even smaller. In other embodiments, ionization potential of the matrix can be close to or near the energy level of the LUMO of the dopant. For example, the ionization potential of the matrix can be within about 0 to about 0.5 eV, about 0 to about 0.3 eV, about 0 to about 0.2 eV, or about 0 to about 0.1 eV of the LUMO energy level of the dopant.

[0032]   The HOMO and LUMO energy levels for various compounds, can be measured, or estimated, according to several techniques known in the art. The two common methods for estimating HOMO energy levels include solution electrochemistry, such as cyclic voltammetry, and ultraviolet photoelectron spectroscopy (UPS). Two methods for estimating LUMO levels include solution electrochemistry and inverse photoemission spectroscopy.

[0033]   Cyclic voltammetry is one of the most common methods for determining oxidation and reduction potentials of compounds. This technique is well known to those skilled in the art. A test compound is dissolved along with a high concentration of electrolyte. Electrodes are inserted and the voltage scanned in either the positive or negative direction (depending on whether an oxidation or reduction is being performed). The presence of a redox reaction is indicated by current flowing through the cell. The voltage scan is then reversed and the redox reaction is reversed. The reference can be an

external electrode, such as Ag/AgCl or SCE, or it can be an internal one, such as ferrocene, which has a known oxidation potential. The latter is often preferred for organic solvents, since the common reference electrodes are water based. A useful parameter that may come from cyclic voltammetry is the carrier gap. If both the reduction and oxidation are reversible, one can determine the energy difference between the hole and the electron (i.e. taking an electron out of the HOMO versus putting one into the LUMO). This value can be used to determine the LUMO energy from a well defined HOMO energy. Methods for determining redox potentials and reversiblity of redox events using cyclic voltammetry are well known in the art.

[0034]   UPS is an alternative technique for determining absolute binding energies in the solid state. Although solution electrochemistry is typically adequate for most compounds, and for giving relative redox potentials, the measurements taken in the solution phase can differ from values in the solid phase. A preferred method of estimating HOMO energies, or ionization potentials, in the solid state is UPS. This is a photoelectric measurement, where the solid is irradiated with UV photons. The energy of the photons are gradually increased until photogenerated electrons are observed. The onset of ejected electrons gives the energy of the HOMO. The photons at that energy have just enough energy to eject an electron from the top of the filled levels. UPS provides HOMO energy level values in eV relative to vacuum which corresponds to the binding energy for the electron.

[0035]   Inverse photoemission may be used to directly estimate LUMO energy levels. This technique involves pre-reducing the sample and then probing the filled states to estimate the LUMO energies. More specifically, a material is injected with electrons which then decay into unoccupied states and emit light. By varying the energy of the incoming electrons and the angle of the incident beam, electronic structure of a material can be studied. Methods of measuring LUMO energy levels using inverse photoemission are well known to those skilled in the art.

[0036]   According to embodiments of the present invention, the doped organic matrix has higher, or improved, conductivity relative to undoped organic matrix. Conductivity of charge transporting materials can be measured by any means available in the art. For example, conductivity of a substance can be determined by measuring resistivity between two leads affixed across the substance. Alternatively, a four probe

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method involves passing a fixed current across a substance between a first pair of leads and then measuring the voltage drop between a second pair of leads situated between the first pair. In this way, the measurement is independent of the resistance in the leads and the relationship V=IR applies.

[0037]   Suitable dopants are preferably stable after electron transfer to or from the matrix. For example, suitable dopants of electron transporting materials preferably remain stable when oxidized. Similarly, suitable dopants of hole transporting materials preferably remain stable when reduced. By the term "stable" is meant that dopants undergo little or no decomposition or chemical changes (such as structural rearrangement) after oxidation or reduction. Alternatively, if dopants undergo decomposition upon oxidation or reduction, it is preferred that the decomposition products be benign or redox inactive materials that preferably do not interfere with, or alter, charge conduction in the matrix material. It is also preferred that dopants be thermally stable, for example, up to temperatures typically encountered in organic light emitting devices, such as for example, about 100, 200, or 300 °C.

[0038]   Dopants can be present in the organic matrix material in an amount sufficient to increase conductivity relative to undoped organic matrix. Dopant quantities can range, for example, from about 0.001 to about 50 % by weight. According to some embodiments, organic matrix is doped, for example, from about 0.05 to about 25, 0.05 to about 10, or from 0.05 to about 1 % by weight. The more efficient the charge transfer between dopant and matrix, the less dopant is required to obtain the desired increase in conductivity.

[0039]   Additionally, dopant can be covalently attached to the organic matrix. For example, dopant can be a substituent attached to a polymeric organic matrix. Accordingly, the level of such doping can be controlled by the amount of substitution on the polymeric organic matrix. Techniques for the attachment of dopant to polymeric organic matrix are well known in the art.

[0040]   Dopants, in accordance with embodiments of the present invention, can be redox tuned. By "redox tuning" is meant the raising or lowering of redox potentials, and, hence, HOMO/LUMO energy levels, by chemical modification of select chemical components of the dopants. For example, a metal-containing dopant can be redox tuned by variation of a metal atom component while keeping the basic structure (e.g.,

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coordination geometry, etc.) of the molecule substantially the same. Similarly, variation of chemical substituents on ligands or organic molecules can also be used in redox tuning. Possessing multiple sites amendable to substitution or replacement, organometallic compounds can be readily tuned. For example, both metal and ligand sites can be varied, allowing multiple degrees of control in designing a dopant having a desired redox potential. Organic compounds having numerous substitutable sites can also allow precise redox tuning. Accordingly, sets of organic and organometallic dopants can be constructed having different substitutions and representing a range of HOMO/LUMO energies. Thus, for any given organic matrix, dopants can be selected or designed according to the HOMO or LUMO energy levels desired for improving the conducting properties of the matrix.

[0041]   Accordingly, the present invention provides for methods of selecting a dopant for increasing the conductivity of an organic matrix of an electron transporting material. The method comprises determining the ionization potential of the dopant; determining the LUMO energy level of the organic matrix; and selecting the dopant if the ionization potential is lower than the LUMO energy level, or if the ionization potential is within about 0 to about 0.5 eV of the LUMO energy level. The method can also include the optional steps of determining the stability of oxidized dopant, and selecting the dopant if it is stable in oxidized form.

[0042]   Conversely, the present invention provides for methods of selecting a dopant for increasing the conductivity of an organic matrix of a hole transporting material. The method comprises determining the ionization potential of the matrix; determining the LUMO energy level of the dopant; and selecting the dopant if the ionization potential is lower than the LUMO energy level, or if the ionization potential is within about 0 to about 0.5 eV of the LUMO energy level. The method can also include the optional steps of determining the stability of reduced dopant, and selecting the dopant if it is stable in reduced form.

[0043]   The present invention provides for, *inter alia*, charge transporting materials, such as electron transporting materials and hole transporting materials, containing an organic matrix and an organometallic dopant. As used herein, the term "organometallic" refers to compounds containing at least one metal-carbon bond. According to some embodiments, organometallic compounds include one, two, three, or

four ligands that each form a metal-carbon bond. Organometallic compounds are well recognized in the art and their chemistry well developed. An overview of organometallic chemistry and examples of organometallic compounds can be found, for example, in Miessler, *et al.*, *Inorganic Chemistry*, 2nd ed., Prentice Hall, Upper Saddle River, NJ, Chapter 13; *Comprehensive Organometallic Chemistry: The Synthesis, Reactions and Structures of Organometallic Compounds*, Vols. 1-9, Wilkinson, ed., Pergamon Press, Oxford, 1982; and *Comprehensive Organometllic Chemistry –II*, Vols. 1-14, Abel, ed., Pergamon Press, Oxford, 1995, each of which is incorporated herein by reference in its entirety.

[0044]   Ligands (L) that can bind to metals through one or more carbon atoms are numerous, and include, for example, carbonyl, thiocarbonyl, cyanide, isocyanide, carbene, carbyne, acyl, alkyl, alkenyl, alkynyl, ketone, carborane, and aromatic compounds, and others. Bonding between metal and carbon can include sigma bonding, pi bonding, or a combination of both. Many unsaturated ligands can form pi complexes with metals. Examples of such complexes include η^2-, η^4-, or η^6-arene, η^5-cyclopentadienyl (Cp), η^3-enyl (such as η^3-allyl), η^2-ketone, π-alkene, and π-alkyne (such as π-acetylene) complexes. Examples of organometallic compounds containing these and other ligands are described in, for example, Collman, *et al.*, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Vally, California, 1987; *Comprehensive Organometallic Chemistry: The Synthesis, Reactions and Structures of Organometallic Compounds*, Vols. 1-9, Wilkinson, ed., Pergamon Press, Oxford, 1982; and *Comprehensive Organometllic Chemistry –II*, Vols. 1-14, Abel, ed., Pergamon Press, Oxford, 1995, each of which is incorporated herein by reference in its entirety.

[0045]   Organometallic compounds include at least one metal atom (M), including both mononuclear and polynuclear compounds. Polynuclear compounds can include, for example, binuclear, trinuclear, tetranuclear, and higher order clusters. M can be any metal atom, including transition metals, lanthanides, actinides, main group metals, alkali metals and alkaline earth metals. First row transition metals include any of Sc, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, and Zn. Second row transition metals include any of Zr, Nb, Mo, Tc, Ru, Rh, Pd, Ag, and Cd, and third row transistion metals include any of La, Hf, Ta, W, Re, Os, Ir, Pt, Au, and Hg. Main group metals include Al, Ga, Ge, In, Sn, Sb, Tl, Pb, Bi,

and Po. In many embodiments, M is a transition metal, such as from any of Groups 5, 6, 7, and 8 of the periodic table. In some embodiments, M can be Cr, Fe, Co, Os, or V. Often, heavy metals, such as, for example, the second and third row transition metals, lanthanides, actinides, as well as fourth and fifth row main group metals can provide thermal stability to organometallic compounds.

[0046]   Organometallic compounds, in addition to having one or more ligands that form metal-carbon bonds, can often include any number of further ligands (X). For example, organometallic compounds can have one, two, three, four, five, or six ligands in addition to those that form metal-carbon bonds. Numerous ligands are known to those skilled in the art and many suitable examples are provided, for example, in Cotton and Wilkinson, *Advanced Inorganic Chemistry*, Fourth Ed., John Wiley & Sons, New York, 1980; *Comprehensive Organometallic Chemistry: The Synthesis, Reactions and Structures of Organometallic Compounds*, Vols. 1-9, Wilkinson, ed., Pergamon Press, Oxford, 1982; and *Comprehensive Organometllic Chemistry –II*, Vols. 1-14, Abel, ed., Pergamon Press, Oxford, 1995; each of which is incorporated herein by reference in its entirety. Further ligands (X) can be monodentate, bidentate, multidentate, π-bonding, organic, inorganic, charged, or uncharged. Ligands often include one or more heteroatoms through which the metal atom can coordinate. Coordinating heteroatoms of the ligands can include oxygen, nitrogen, sulphur, phosphorus, and the like. Nitrogen-containing ligands can include amines, nitrenes, azide, diazenes, triazenes, nitric oxide, polypyrazolylborates, heterocycles such as 2,2'-bipyridine (bpy), 1,10-phenanthroline, terpyridine (trpy), pyridazine, pyrimidine, purine, pyrazine, pyridine, 1,8-napthyridine, pyrazolate, imidazolate, and macrocycles including those with and without a conjugated π system, and the like. Preferred nitrogen-containing ligands include those that contain one or more heterocycles such as pyridine and polypyridyl ligands such as terpyridine (trpy), bipyridine (bpy), and derivatives thereof. Phosphorus-containing ligands typically include phosphines and the like. Oxygen-containing ligands include water, hydroxide, oxo, superoxide, peroxide, alkoxides, alcohols, aryloxides, ethers, ketones, esters, carboxylates, crown ethers, β-diketones, carbamate, dimethylsulfoxide, and oxo anions such as carbonate, nitrate, nitrite, sulfate, sulfite, phosphate, perchlorate, molybdate, tungstate, oxalate and related groups. Sulfur-containing ligands can include hydrogen

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sulfide, thiols, thiolates, sulfides, disulfides, thioether, sulfur oxides, dithiocarbamates, 1,2-dithiolenes, and the like. Hydrogen and halides can also serve as ligands.

[0047]   According to embodiments of the present invention, charge transporting materials can contain, as a dopant, an organometallic compound having at least one cyclopentadienyl (Cp, η^5-C_5H_5) ligand, or derivative thereof.   In this regard, organometallic complexes having one, two, three, four or more Cp ligands are suitable. Cyclopentadienyl metal complexes are well known in the art and constitute a large body of known organometallic compounds.   Synthetic methods for preparing Cp organometallic complexes have been well studied.   For example, many Cp metal complexes can be prepared by combining cyclopentadienyl anion with substitution-labile metal halides.   Organometallic complexes containing substituted Cp ligands can be typically made in the same manner as for any known Cp complex by replacing Cp with the substituted Cp during synthesis. Cyclopentadienyl organometallic compounds, their chemistry, and methods for their synthesis are described in, for example, Strelets, *et al.*, *Coordination Chemical Reviews*, **1992**, *114*, 1-60; *Comprehensive Organometallic Chemistry: The Synthesis, Reactions and Structures of Organometallic Compounds*, Vols. 1-9, Wilkinson, ed., Pergamon Press, Oxford, 1982; and *Comprehensive Organometallic Chemistry –II*, Vols. 1-14, Abel, ed., Pergamon Press, Oxford, 1995; and Collman, *et al.*, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Vally, California, 1987, each of which is incorporated herein by reference in its entirety.

[0048]   The Cp ligand can be derivatized by incorporating one or more substituents. Substituents can include, for example, H, electron withdrawing substituents, or electron donating substituents. Derivatization can lead to changes in the compounds' electronic properties, by either raising or lowering redox potentials, thereby modifying the HOMO/LUMO energy levels.   Substitution of Cp and the preparation of organometallic complexes containing substituted Cp are well known in the art and many Cp derivatives are commercially available. Examples of some known Cp derivatives include pentamethylcylcopentadiene (Cp*), aryl-Cp: $C_5Ar_{5-n}H_n$ (n = 1-5), nitro-Cp: $C_5(NO_2)_{5-n}H_n$ (n = 3, 4), formyl-Cp: $C_5(CHO)_{5-n}H_n$ (n = 3, 4), cyano-CP: $C_5(CN)_{5-n}H_n$ (n = 2, 3, 4) and trifuoromethyl-Cp: $C_5(CF_3)_{5-n}H_n$ (n = 2, 3, 4). Derivatization of Cp is well described in the literature such as, for example, in *Comprehensive Organometallic*

Chemistry: The Synthesis, Reactions and Structures of Organometallic Compounds, Vols. 1-9, Wilkinson, ed., Pergamon Press, Oxford, 1982; and *Comprehensive Organometallic Chemistry –II*, Vols. 1-14, Abel, ed., Pergamon Press, Oxford, 1995, each of which is incorporated herein by reference in its entirty. According to some embodiments, the Cp ligands can include more than one substituent. Ligands having more than one substituent can include any combination of different substituents. For example, Cp ligands can contain any number of, and any combination of, H, electron withdrawing groups, and electron donating groups. Additionally, each Cp ligand, in organometallic compounds having more than one, can be substituted differently. As used herein, the phrases "Cp ligand" and "cyclopentadienyl ligand" are meant to refer to both substituted and unsubstituted versions of the ligand.

[0049]   Substituents that can serve as electron withdrawing and donating groups are well known in the art. An electron withdrawing group is any group that withdraws, usually inductively, electron density away from the molecule to which it is attached. Conversely, an electron donating group is any group that donates electron density, usually either inductively or by resonance effect, to the molecule to which it is attached. When a substituent is attached to a non-aromatic molecule, electron withdrawing or donating ability is believed to be primarily governed by inductive effects. Thus, the electronegativites of a substituent and the atom to which it is attached can control electron withdrawing or donating ability. When a substituent is attached to an aromatic compound, such as phenyl or the anion of cyclopentadiene, it is believed that a resonance effect contributes to electron withdrawing and donating ability. Often, substituents with a lone pair of electrons act as electron donating substituents because the lone pair can be delocalized onto the aromatic molecule. Thus, halogen substituents, while strongly electronegative, can act as electron donating substituents in aromatic systems. Numerous techniques for determining whether a substituent has an electron withdrawing or donating effect are well known in the art. For example, measurements of either or both inductive and resonance effects can be carried out by appropriate spectroscopic methods. Electron withdrawing and donating groups are well described in, for example, March, *Advanced Organic Chemistry*, 3rd ed., John Wiley & Sons, New York, 1985.

[0050]   Some examples of electron withdrawing substituents include aryl, cyano, nitro, carbonyl, aldehyde, carboxylic acid, alkoxycarbonyl, aminocarbonyl, alkylsufonyl,

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alkoxysulfonyl, nitrosyl, tricyanoethyenyl, and alkyl substituted by halo, such as perfluoroalkyl, to name a few. Halogen can also be electron withdrawing.

[0051]   Some examples of electron donating groups include alkyl, alkoxy, amino, alkylamino, dialkylamino, mercapto, phosphino, oxo, sulfido, thiolato, amido, hydroxyl, silyl, and alkylcarbonyloxy, to name a few. Halogen can often be electron donating when attached to an aromatic molecule.

[0052]   Numerous classes of organometallic complexes containing at least one Cp ligand are known and are suitable as dopants according to embodiments of the present invention. One such class includes the metallocenes which are characterized as having a metal atom "sandwiched" between two substantially parallel cyclopentadienyl ligands. Some metallocenes have been prepared using, for example, the metals V, Cr, Mn, Fe, Co, and Ni. Metallocenes are well known in the art and their synthesis, structure, and reactivity are well described in, for example, Togni, *et al.*, *Metallocenes*, Wiley, New York, 1998; Strelets, *Coordination Chemical Reveiws*, **1992**, *114*, 1-60; *Comprehensive Organometallic Chemistry: The Synthesis, Reactions and Structures of Organometallic Compounds*, Vols. 1-9, Wilkinson, ed., Pergamon Press, Oxford, 1982; and *Comprehensive Organometallic Chemistry –II*, Vols. 1-14, Abel, ed., Pergamon Press, Oxford, 1995; Collman, *et al.*, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Vally, California, 1987, and Cotton, *et al.*, *Advanced Inorganic Chemistry*, Fourth ed., John Wiley & Sons, New York, 1980, each of which is incorporated herein by reference in its entirety.

[0053]   The oxidation potential of metallocenes can be readily tuned by choice of metal. For example, the oxidation potential of ferrocene (Cp_2Fe) is about 0.45 V (v. SCE) with an ionization potential of about 4.8 eV (as measured by UPS). By substituting iron for cobalt, resulting in cobaltocene (Cp_2Co), a lower oxidation potential of about –0.94 V (ionization potential of 3.4 eV based on Cp_2Fe) can be obtained. Similarly, substituting the Fe in ferrocene with Cr results in a metallocene (Cp_2Cr) with a lowered oxidation potential of about –0.55 V (ionization potential of 3.8 eV). As the LUMO energies of typical electron transporting materials can range from about 2.5 to about 4.0 eV, metallocenes can make suitable n-type dopants.

[0054]   It is also possible to tune the redox properties of metallocenes by substitution of the cyclopentadienyl ligands. Oxidation potential of ferrocene and

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cobaltocene can be lowered by incorporating electron donating groups, such as methyl substituents, on the Cp ligands. For example, the oxidation potential of ferrocene in which the hydrogens of the Cp ligands have all been replaced with methyl (Cp*) is lowered to about –0.12 V and the corresponding cobaltocene (Cp*$_2$Co) has an oxidation potential lowered to about –1.47 V, leading to an estimated HOMO energy (or ionization potential) of about 2.9 eV. Similarly, substituting the Cp groups with an electron withdrawing group, such as phenyl, can lead to an increased oxidation potential. Intermediate substitution, i.e., using fewer than five methyl groups per Cp ligand, can give intermediate shifts in redox potential. Thus, by both variation of metal and ligand substitution, a set of metallocenes representing a full range of oxidation potentials, and hence, ionization energies can be accessed. Accordingly, the set of metallocenes can provide at least one dopant having a desirable ionization energy for improving the conductivity for any given charge transporting material, such as, for example, an electron transporting material.

[0055]   Some metallocene dopants suitable in embodiments of the present invention can be represented by the formula $M(L^1)(L^2)$. L^1 and L^2 are formally anionic cyclopentadienyl ligands having the formulas designated below.
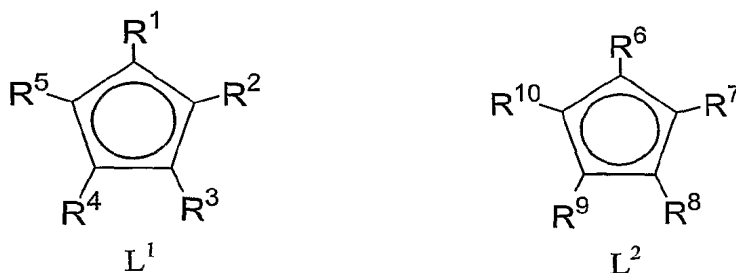
M can be any metal atom. According to some embodiments, M can be a transition metal, such as, for example, Fe, Co, or Cr.

[0056]   The cyclopentadienyl ligands are substituted by substituents R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10}, which can be each, independently, H, an electron withdrawing substituent, or an electron donating substituent. In some embodiments, at least one of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is an electron withdrawing group or electron donating group. In some embodiments, at least one R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is alkyl, alkoxy, amino, mercapto, or phosphino. In other embodiments, at least one R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is aryl, cyano, nitro, carbonyl, tricyanoethyenyl, or perfluoroalkyl. In further embodiments, at least one R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9,

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and R^{10} is halogen. Any combination of H, electron withdrawing groups, and electron donating groups can be suitable.

[0057]   According to some embodiments, the cyclopentadienyl ligands L^1 and L^2 can be covalently linked by one or more linking groups. Linkage of the two Cp ligands can modify stereochemistry of the metallocene, thereby modifying HOMO/LUMO energy levels and providing another means for tuning redox potential. Any linking group can be suitable, including linking groups having alkyl, aryl, and silyl moieties.

[0058]   Besides the metallocenes, numerous other organometallic compounds containing at least one cyclopentadienyl ligand can be suitable in embodiments of the present invention. For example, organometallic compounds containing at least one cyclopentadienyl ligand and at least one other ligand (X), such as represented by the formula $M(L^1)_n(X)_m$, can be used as dopants. According to this formula, metal atom M and cyclopentadienyl ligand L^1 are as defined hereinbefore. Ligand X can be any ligand as described hereinbefore, including both mono- and polydentate ligands. The number of L^1 and X ligands can vary and are designated by n and m respectively. The sum of n and m can range from 2 to about 6. The values for n and m can range from 1 to about 5.

[0059]   Some examples of organometallic compounds having formula $M(L^1)_n(X)_m$ include those where n is 2. Such complexes can include the so-called "bent sandwich" complexes in which the two cyclopentadienyl ligands are not parallel. "Bent sandwich" compounds are well known in the art and their chemistry is described, for example, in *Comprehensive Organometallic Chemistry: The Synthesis, Reactions and Structures of Organometallic Compounds*, Vols. 1-9, Wilkinson, ed., Pergamon Press, Oxford, 1982; and *Comprehensive Organometallic Chemistry –II*, Vols. 1-14, Abel, ed., Pergamon Press, Oxford, 1995; and Collman, *et al., Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Vally, California, 1987; and Cotton, *et al., Advanced Inorganic Chemistry*, Fourth ed., John Wiley & Sons, New York, 1980, Ch. 27, each of which is incorporated herein by reference in its entirety. In many of these complexes, each X can be, independently, for example, halogen, hydrogen, carbonyl, alkyl, or alkenyl. Variable m can range from 1 to about 3. Some examples of $M(L^1)_n(X)_m$ compounds include Cp_2TiCl_2, Cp_2WH_2, and others.

[0060]   Some examples of organometallic compounds having formula $M(L^1)_n(X)_m$ include those where n is 1. Such complexes can include the so-called "half sandwich"

compounds, many having a "piano stool" structure. The "half sandwich" complexes are well known in the art and well described in, for example, *Comprehensive Organometallic Chemistry: The Synthesis, Reactions and Structures of Organometallic Compounds*, Vols. 1-9, Wilkinson, ed., Pergamon Press, Oxford, 1982; and *Comprehensive Organometallic Chemistry –II*, Vols. 1-14, Abel, ed., Pergamon Press, Oxford, 1995; and Collman, *et al.*, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Vally, California, 1987, each of which is incorporated herein by reference in its entirety. Examples of such compounds include those where, for example, each X is, independently, carbonyl, nitrosyl, halogen, phosphine, alkyl, or aryl and *m* can range from 1 to about 4. Some examples of monocyclopentadienyl organometallic compounds include, $CpMo(CO)_3Cl$, $CpMo(CO)_2NO$, $CpMo(CO)_3H$, $CpMo(CO)_3(alkyl)$, and the like.

[0061]   Other suitable organometallic compounds containing at least one cyclopentadienyl ligand include polynuclear complexes having more than one metal center. For example, polynuclear complexes can be dimers or trimers of any of the above described cyclopentadienyl complexes.

[0062]   According to some embodiments of the present invention, charge transporting materials can include an organic matrix and a dopant having the formula $M(Ar)_4$. The metal atom M can be any metal atom, including transition metals. Examples of transition metals include metals of Groups 5, 6, 7, or 8. Os or V can be particularly suitable, for example. The synthesis and reactivity of $M(Ar)_4$ compounds is well known in the art.

[0063]   Ar can be an aryl group substituted by one or more substitutents R^{11}. Any aryl group is suitable. Some examples of suitable aryl groups in compounds having the formula $M(Ar)_4$ include phenyl, naphthyl, biphenyl, anthracenyl, and fluorenyl. In many suitable embodiments, each Ar is bonded to M through one atom of the Ar group (η^1-bonding). According to further embodiments, the four Ar groups can be substituted differently from each other.

[0064]   Each individual R^{11} can be, independently, H, an electron withdrawing substituent, or an electron donating substituent. Any number of different or the same R^{11} substituents can be present on the aryl group, including various combinations of H, electron withdrawing groups, and electron donating groups. In some embodiments, at least one R^{11} is an electron withdrawing group or an electron donating group. Examples

of R^{11} substituents include alkyl, alkoxy, amino, mercapto, or phosphino. Further examples of R^{11} substituents include aryl, cyano, nitro, carbonyl, tricyanoethyenyl, or perfluoroalkyl. R^{11} can also be halogen.

[0065]   In further embodiments according to the present invention, charge transporting materials can include an organometallic dopant having at least one arene ligand. Arene ligands are typically benzenoid ligands that form pi complexes with metal atoms. η6-Arene complexes are well known in the art and discussed in detail for example, in Cotton, *et al., Advanced Inorganic Chemistry*, Fourth ed., John Wiley & Sons, New York, 1980, Ch. 27, which is incorporated herein by reference in its entirety. As with Cp ligands, arene ligands can be substituted by any number and combination of H, electron withdrawing groups, and electron donating groups. Some examples of organometallic compounds containing at least one arene ligand include, $(C_6H_6)_2Cr$, $(C_6H_6)Cr(CO)_3$, $(C_6(CH_3)_6)_2Mn$, $(C_6H_6)_2Ti$, $(p-C_6H_4F_2)_2V$, $(C_6H_6)_2Nb$, $(C_6H_6)_2W$, $(C_6H_6)_2Ru$, $(C_6H_6)_2Hf(PMe_3)$, and derivatives thereof. η4-Arene complexes can also be suitable.

[0066]   Suitable organometallic dopants of the present invention can also include at least one heterocylic analog of an arene or cyclopentadienyl ligand. Examples of heterocyclic analogs include the anion of thiophene and derivatives thereof, the anion of pyrrole and derivatives thereof, pyridines, boroles, borazines, borazoles, and substituted derivatives thereof. As with Cp and arene ligands, the heterocyclic analogs can include any number, and any combination, of substituents including H, electron withdrawing groups, and electron donating groups. Organometallic complexes containing heterocyclic analogs of Cp and arene ligands are well known in the art and described, for example, in Cotton, *et al., Advanced Inorganic Chemistry*, John Wiley & Sons, New York, 1980, Ch. 27. Examples of such compounds include $(C_4Ph_4BPh)Ni(CO)_2$ and others.

[0067]   Suitable organometallic dopants of the present invention can also contain at least one carborane ligand. Some suitable carborane ligands include $B_9C_2H_{11}{}^{2-}$, $B_7C_2H_{11}{}^{2-}$, and others. Typically, one or two carborane ligands can coordinate to a metal atom, often in an analogous manner to cyclopentadienyl. Carborane ligands can be readily derivatized to include one or more electron withdrawing groups or electron donating groups. Organometallic compounds containing carborane ligands are well known in the art and their synthesis and reactivity are well described in, for example,

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Cotton, *et al., Advanced Inorganic Chemistry*, John Wiley & Sons, New York, 1980, Ch. 27, which is incorporated herein by reference in its entirety.

[0068]   Embodiments according to the present invention further include charge transporting materials containing an organic dopant. In some embodiments, the organic dopant can include naphthylimide derivatives having formula I.

I
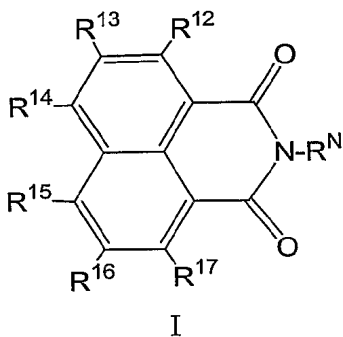
Substituents R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{N} of the naphthylimide core can be each, independently, H, an electron withdrawing substituent, or an electron donating substituent. Any number of, and any combination of, H, electron withdrawing substituents, or electron donating substituents is suitable. In some embodiments, at least one R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{N} is an electron withdrawing group or an electron donating group. Accordingly, in some embodiments, at least one R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{N} is alkyl, alkoxy, amino, mercapto, or phosphino. In other embodiments, at least one R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{N} is aryl, cyano, nitro, carbonyl, tricyanoethyenyl, or perfluoroalky. In yet further embodiments, at least one R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{N} can be halogen. According to some embodiments, R^{N} can be aryl, alkyl, perfluoroalkyl, or a substituent of formula II.

II
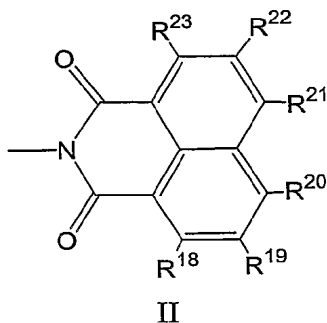
Each R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, and R^{23} can be, independently, H, an electron withdrawing substituent, or an electron donating substituent.

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[0069]   Naphthylimides and other similar organic compounds can be modified by methods well known in the art. For example, in formulas I and II, each R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^N, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, and R^{23} can be substituted or modified by techniques well known in the art.

[0070]   The naphthylimides of formula I can be used as p-type dopants in hole transporting materials. Unsubstituted naphthylimide (where R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^N are each H) has an estimated LUMO energy of about 4.2 eV (estimated from electrochemical data). Lower LUMO energies can be obtained by substitution with fluoro or other groups such as NO_2, CN, CF_3, CHO, and the like. Combination of various groups, including both electron withdrawing and electron donating substituents, can effectively tune the naphthylimide redox potential to any desired value appropriate for a given organic matrix.

[0071]   The present invention further provides for charge transporting materials containing an organic matrix and an organic or organometallic dopant that is incapable of transferring charge to the organic matrix except when the dopant is optically excited. According to some embodiments, the charge transporting material containing such a dopant can be an electron transporting material in which the optically excited dopant reduces the organic matrix. Often, such a dopant is chemically altered after transfer of charge to the matrix such that back electron transfer is prevented. For example, the dopant can structurally rearrange or irreversibly decompose into one or more compounds that have different redox properties from the original dopant molecule. In some embodiments, decomposition products are not redox active and/or are not capable of reversible redox processes. Such dopants can be useful in preparing charge transporting materials in which doping can be switched on by optical excitation. Hence, conductivity and other properties of charge transporting materials, and the properties of devices that include them, can be optically controlled.

[0072]   Dopants capable of transferring charge to organic matrix upon optical excitation can include both organic and organometallic compounds. According to some embodiments, optically activated dopants are capable of transferring electrons to organic matrix and are thereby suitable in electron transporting materials. Optically activated dopant can include many organometallic compounds such as, for example, Ir, Re, Os, Pt, or Au complexes.

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[0073]   The present invention further provides for organic light emitting devices containing at least one doped charge transporting material. For example, OLEDs can include a charge transporting layer having an organic matrix doped with any of the dopants, or derivatives thereof, described herein. The charge transporting layer can be a hole transporting layer or an electron transporting layer. According to some embodiments, OLEDs can have both doped hole and doped electron transporting layers. OLEDs of the present invention can further include any number of additional layers including, for example, hole injecting, hole blocking, electron injecting, electron blocking, luminescent, and other layers.

[0074]   Light emitting devices of the present invention can be fabricated by a variety of techniques well known to those skilled in the art. Small molecule layers, including those made of neutral metal complexes and doped materials, can be prepared by vacuum deposition, organic vapor phase deposition (OVPD), such as disclosed in U.S. Pat. No. 6,337,102, which is incorporated herein by reference in it its entirety. Other methods include solution processing such as spin coating or CVD. Layers of charged compounds, such as salts of charged metal complexes, can be prepared by solution methods such a spin coating or by an OVPD method such as disclosed in U.S. Pat. No. 5,554,220, which is incorporated herein by reference in its entirety.

[0075]   Devices and techniques for OLED fabrication are described throughout the literature and in, for example, U.S. Pat. Nos. 5,703,436; 5,986,401; 6,013,982; 6,097,147; and 6,166,489. For devices from which light emission is directed substantially out of the bottom of the device (i.e., substrate side), a transparent anode material such as ITO may be used as the bottom electron. A top electrode, which is typically a cathode, may be comprised of a thick and reflective metal layer having a high electrical conductivity. Alternatively, for transparent or top-emitting devices, a transparent cathode may be used such as disclosed in U.S. Pat. Nos. 5,703,436 and 5,707,745, each of which is incorporated herein by reference in its entirety. Top-emitting devices may have an opaque and/or reflective substrate, such that light is produced substantially out of the top of the device. Devices can also be fully transparent, emitting from both top and bottom.

[0076]   Because the doped charge transporting materials can have increased conductivity relative to an undoped organic matrix, the present invention further provides methods for increasing the power efficiency of an organic light emitting device. The

methods comprise the step of incorporating into an organic light emitting device one or more of the doped charge transporting materials according to the present invention. For example, efficiency can be improved by including a doped electron transporting material, a doped hole transporting material, or both, in an OLED. Methods for measuring device efficiencies are well known in the art.

[0077]   Light emitting devices of the present invention can be used in a pixel for a display. Virtually any type of display can incorporate the present devices. Displays can include computer monitors, televisions, personal digital assistants, printers, instrument panels, bill boards, and the like. In particular, the present devices can be used in heads-up displays because they can be substantially transparent when not in use.

[0078]   As used herein, the terms "lower," "less," and "deeper," in reference to molecular orbital energies, are used interchangeably. These terms generally describe molecular orbitals residing at a lower, or more stable, energy levels. Accordingly, orbitals having energy below that of another orbital are lower in energy. Ionization of electrons from lower energy orbitals requires more energy than ionization of electrons in shallower orbitals (orbitals of greater energy). Thus, although the deeper orbitals are said to be lower, they are often referred to numerically by higher numbers. For example, a molecular orbital residing at 5.5 eV is lower (deeper) than a molecular orbital residing at 2.5 eV. Similarly, the terms "shallower," "greater," and "higher," in reference to orbital energy levels, refer to orbitals residing at less stable energies. Accordingly, orbitals having energy above that of another orbital are higher in energy. These terms are well known to those skilled in the art.

[0079]   As used herein, the term "alkyl" includes linear, branched, and cyclic alkyl groups. In some embodiments, alkyl groups are C_1-C_{20} alkyl groups. Examples of alkyl groups include, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, cyclohexyl, norbornyl, and the like. "Alkenyl" groups refer to alkyl groups having one or more double bonds, and "alkynyl" groups refer to alkyl groups having one or more triple bonds. "Alkoxy" groups can have from about 1 to about 20 carbon atoms and can include, for example, methoxy, ethoxy, propoxy, n-butoxy, isobutoxy, and the like. "Aryloxy" groups can have from about 3 to about 40 carbon atoms and can include, for example, phenoxy and the like. "Aryl" groups can be any mono- or polycyclic aromatic group, and include "heteroaryl" groups which refers to an aryl group including one or more heteroatoms such

as O, S, P or N. Aryl groups can have 3 to about 40 carbon atoms and can include, for example, phenyl, 4-methylphenyl, naphthyl, anthracenyl, phenanthryl, pyridyl, indolyl, benzothiophene, quinolinyl, and the like. "Amino" groups, as used herein, include amino, alkylamino, dialkylamino, arylamino, and diarylamino groups. Examples of amino groups include, NH_2, methylamino, dimethylamino, phenylamino, diphenylamino, and the like. "Phosphino" groups, as used herein, include phosphino, alkylphosphino, dialkylphosphino, arylphosphino, and diarylphosphino. Some examples of phosphino groups include PH_2, methylphosphino, dimethylphosphino, phenylphosphino, diphenylphosphino, and the like. "Thiolato" groups can have from about 1 to about 20 carbon atoms and can include, for example, thiomethoxy, thiophenoxy, and the like. "Halo" groups include fluoro, chloro, bromo, and iodo, for instance.

[0080]   As those skilled in the art will appreciate, numerous changes and modifications can be made to the embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.

[0081]   Throughout this specification various groupings are employed to conveniently describe constituent variables of compounds and groups of various related moieties. It is specifically intended that each occurrence of such groups throughout this specification include every possible subcombination of the members of the groups, including the individual members thereof.

[0082]   It is intended that each of the patents, applications, and printed publications mentioned in this patent document be hereby incorporated by reference in its entirety.

EXAMPLES
Example 1:   Electron transporting materials

[0083]   Example matrix/dopant combinations for electron transporting materials of the present invention, according to some embodiments, can include phenanthrenes and/or triazoles as matrix in combination with cobaltenes or chromacenes as dopants.

What is claimed is:

1.   A charge transporting material comprising an organic matrix and an organometallic dopant, wherein said charge transporting material has a higher conductivity than undoped organic matrix.

2.   The charge transporting material of claim 1 wherein said charge transporting material is an electron transporting material.

3.   The charge transporting material of claim 1 wherein said charge transporting material is a hole transporting material.

4.   The charge transporting material of claim 1 wherein said dopant is stable to oxidation or reduction.

5.   The charge transporting material of claim 1 wherein said dopant decomposes to redox inactive materials upon oxidation or reduction.

6.   An electron transporting material comprising an organic matrix and an organometallic dopant, wherein said dopant is capable of transferring electrons to said organic matrix, and wherein said electron transporting material has a higher conductivity than undoped organic matrix.

7.   The electron transporting material of claim 6 wherein said dopant has an ionization potential within about 0 to about 0.5 eV of the LUMO energy level of said organic matrix.

8.   The electron transporting material of claim 6 wherein said dopant has an ionization potential lower than the LUMO energy level of said organic matrix.

9.   The electron transporting material of claim 6 wherein said dopant is stable in oxidized form.

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10.   The electron transporting material of claim 6 wherein said dopant decomposes to redox inactive materials upon oxidation.

11.   The electron transporting material of claim 6 wherein said dopant is present in said organic matrix in an amount of about 0.05 to about 25 percent by weight.

12.   The electron transporting material of claim 6 wherein said organic matrix comprises unsaturated hydrocarbons, unsaturated N- and O-containing heterocycles, or metal complexes.

13.   The electron transporting material of claim 6 wherein said organic matrix comprises phenanthrolines, carbazoles, oxidiazoles, triazoles, triazines, imidazoles, or benzimidazoles.

14.   The electron transporting material of claim 6 wherein said organic matrix comprises bathocuprione, aluminum tris(8-hydroxyquinoline), 4,4'-dicarbazolyl-biphenyl, octaphenylcyclooctatetraene, zirconium tetra(8-hydroxyquinoline), hafnium tetra(8-hydroxyquinoline), 3-phenyl-4-1-naphthyl-5-phenyl-1,2,4-triazole, or 3-(p-tertiary butyl-phenyl)-4-(p-biphenyl)-1,2,-oxidiazole.

15.   The electron transporting material of claim 6 wherein said organic matrix comprises a polymer.

16.   The electron transporting material of claim 15 wherein said dopant is covalently attached to said polymer.

17.   The electron transporting material of claim 15 wherein said polymer is a cyano-substituted polyphenylenevinylene, an oxidiazole-containing polymer, or a triazole-containing polyer.

18.   A hole transporting material comprising an organic matrix and an organometallic dopant, wherein said dopant is capable of transferring holes to said organic matrix, wherein said hole transporting material has higher conductivity than undoped organic matrix.

19.   The hole transporting material of claim 18 wherein said organic matrix has an ionization potential within about 0 to about 0.5 eV of the LUMO energy level of said dopant.

20.   The hole transporting material of claim 18 wherein said organic matrix has an ionization potential less than the LUMO energy level of said dopant.

21.   The hole transporting material of claim 18 wherein said dopant is stable in reduced form.

22.   The hole transporting material of claim 18 wherein said dopant is decomposed to redox inactive materials upon reduction.

23.   The hole transporting material of claim 18 wherein said dopant is present in said organic matrix in an amount of about 0.05 to about 25 percent by weight.

24.   The hole transporting material of claim 18 wherein said organic matrix comprises triarylamines, phthalocyanines, metal phthalocyanines, porphryins, metal porphyrins, indolocarbazoles, metal complexes, iminostilbene containing compounds, or carbazole containing compounds.

25.   The hole transporting material of claim 18 wherein said organic matrix comprises TPD, α-NPD, or β-NPD.

26.   The hole transporting material of claim 18 wherein said organic matrix comprises a polymer.

27.   The hole transporting material of claim 18 wherein said dopant is covalently attached to said polymer.

28.   The hole transporting material of claim 27 wherein said polymer is a polyphenylenevinylene, polyvinylcarbazole, or triarylamine pendant polymer.

29.   A method for selecting an organometallic dopant for increasing conductivity of an organic matrix of an electron transporting material, said method comprising:

determining the ionization potential of said dopant;

determining the LUMO energy level of said organic matrix; and

selecting said dopant if said ionization potential is lower than said LUMO energy level, or if said ionization potential is within about 0 to about 0.5 eV of said LUMO energy level.

30.   A method for selecting an organometallic dopant for increasing conductivity of an organic matrix of a hole transporting material, said method comprising:

determining the ionization potential of said organic matrix;

determining the LUMO energy level of said dopant; and

selecting said dopant if said ionization potential is lower than said LUMO energy level, or if said ionization potential is within about 0 to about 0.5 eV of said LUMO energy level.

31.   A charge transporting material comprising an organic matrix and a dopant, wherein said dopant is an organometallic compound comprising at least one cyclopentadienyl ligand optionally substituted by one or more substituents selected from H, an electron withdrawing substituent, or an electron donating substituent.

32.   The charge transporting material of claim 31 wherein said dopant comprises a transition metal.

33.   The charge transporting material of claim 31 wherein said charge transporting material is an electron transporting material.

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34.   The charge transporting material of claim 31 wherein said charge transporting material is a hole transporting material.

35.   The charge transporting material of claim 31 wherein said cyclopentadienyl ligand is substituted by at least one electron withdrawing substituent or electron donating substituent.

36.   A charge transporting material comprising an organic matrix and a dopant, wherein said dopant is an organometallic compound comprising at least one arene ligand optionally substituted by one or more substituents selected from H, an electron withdrawing substituent, or an electron donating substituent.

37.   The charge transporting material of claim 36 wherein said dopant comprises a transition metal.

38.   The charge transporting material of claim 36 wherein said charge transporting material is an electron transporting material.

39.   The charge transporting material of claim 36 wherein said charge transporting material is a hole transporting material.

40.   The charge transporting material of claim 36 wherein said arene ligand is substituted by at least one electron withdrawing substituent or electron donating substituent.

41.   A charge transporting material comprising an organic matrix and a dopant, wherein said dopant is an organometallic compound comprising at least one carborane ligand optionally substituted by one or more substituents selected from H, an electron withdrawing substituent, or an electron donating substituent.

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42. The charge transporting material of claim 41 wherein said dopant comprises a transition metal.

43. The charge transporting material of claim 41 wherein said charge transporting material is an electron transporting material.

44. The charge transporting material of claim 41 wherein said charge transporting material is a hole transporting material.

45. The charge transporting material of claim 41 wherein said carborane ligand is substituted by at least one electron withdrawing substituent or electron donating substituent.

46. A charge transporting material comprising an organic matrix and a dopant, wherein said dopant is a metallocene having the formula $M(L^1)(L^2)$, wherein L^1 has the formula:
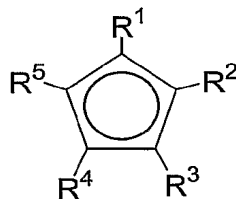
and L^2 has the formula:

wherein:

each R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is, independently, H, an electron withdrawing substituent, or an electron donating substituent; and

M is a metal atom.

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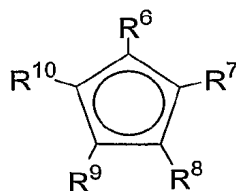
47.   The charge transporting material of claim 46 wherein M is a transition metal.

48.   The charge transporting material of claim 46 wherein M is Fe, Co, or Cr.

49.   The charge transporting material of claim 46 wherein at least one R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is an electron withdrawing substituent.

50.   The charge transporting material of claim 46 wherein at least one R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is an electron donating substituent.

51.   The charge transporting material of claim 46 wherein at least one R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is alkyl, alkoxy, amino, mercapto, or phosphino.

52.   The charge transporting material of claim 46 wherein at least one R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is aryl, cyano, nitro, carbonyl, tricyanoethenyl, or perfluoroalkyl.

53.   The charge transporting material of claim 46 wherein at least one R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and R^{10} is halogen.

54.   The charge transporting material of claim 46 wherein L^1 and L^2 are covalently linked by a linking group.

55.   The charge transporting material of claim 46 wherein said linking group comprises an alkyl, aryl, or silyl group.

56.   The charge transporting material of claim 46 wherein said charge transporting material is an electron transporting material.

57.   A charge transporting material comprising an organic matrix and a dopant, wherein said dopant has the formula $M(Ar)_4$, wherein M is a metal atom, Ar is an aryl

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group substituted by one or more R^{11}, wherein each R^{11} is, independently, H, an electron withdrawing substituent, or an electron donating substituent.

58.   The charge transporting material of claim 57 wherein M is a transition metal.

59.   The charge transporting material of claim 57 wherein M is a Group 5, 6, 7, or 8 transition metal.

60.   The charge transporting material of claim 57 wherein M is V or Os.

61.   The charge transporting material of claim 57 wherein Ar is phenyl, naphthyl, biphenyl, anthracenyl, or fluorenyl.

62.   The charge transporting material of claim 57 wherein at least one R^{11} is an electron withdrawing group.

63.   The charge transporting material of claim 57 wherein at least one R^{11} is an electron donating group.

64.   The charge transporting material of claim 57 wherein at least one R^{11} is alkyl, alkoxy, amino, mercapto, or phosphino.

65.   The charge transporting material of claim 57 wherein at least one R^{11} is halogen.

66.   The charge transporting material of claim 57 wherein at least one R^{11} is aryl, cyano, nitro, carbonyl, tricyanoethenyl, or perfluoroalkyl.

67.   The charge transporting material of claim 57 wherein said charge transporting material is an electron transporting material.

68.   The charge transporting material of claim 57 wherein said charge transporting material is a hole transporting material.

69. A charge transporting material comprising an organic matrix and a dopant, wherein said dopant has the formula:
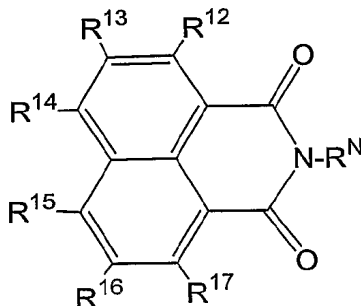
wherein each R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^N is, independently, H, an electron withdrawing substituent, or an electron donating substituent.

70. The charge transporting material of claim 69 wherein at least one R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^N is an electron withdrawing substituent.

71. The charge transporting material of claim 69 wherein at least one R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^N is an electron donating substituent.

72. The charge transporting material of claim 69 wherein at least one R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^N is alkyl, alkoxy, amino, mercapto, or phosphino.

73. The charge transporting material of claim 69 wherein at least one R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^N is halogen.

74. The charge transporting material of claim 69 wherein at least one R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^N is aryl, cyano, nitro, carbonyl, tricyanoethyenyl, or perfluoroalkyl.

75. The charge transporting material of claim 69 wherein R^N is aryl, alkyl, or perfluoroalkyl.

76.   The charge transporting material of claim 69 wherein R^N is a substituent of the formula:
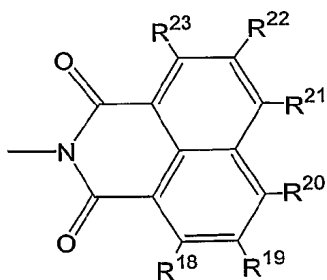
wherein:

each R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, and R^{23} is, independently, H, an electron withdrawing substituent, or an electron donating substituent.

77.   The charge transporting material of claim 69 wherein said charge transporting material is a hole transporting material.

78.   A charge transporting material comprising an organic matrix and a dopant, wherein said dopant is incapable of transferring charge to said organic matrix except when said dopant is optically excited.

79.   The charge transporting material of claim 78 wherein said charge transporting material is an electron transporting material.

80.   The electron transporting material of claim 78 wherein said optically excited dopant transfers electrons to said organic matrix.

81.   The electron transporting material of claim 78 wherein said dopant is chemically altered upon oxidation.

82.   The electron transporting material of claim 78 wherein said dopant is an organometallic compound comprising Ir, Re, Os, Pt, or Au.

83.   An organic light emitting device comprising the charge transporting material of claim 1.

84.   An organic light emitting device comprising the electron transporting material of claim 6.

85.   An organic light emitting device comprising the hole transporting material of claim 18.

86.   An organic light emitting device comprising the charge transporting material of claim 31.

87.   An organic light emitting device comprising the charge transporting material of claim 36.

88.   An organic light emitting device comprising the charge transporting material of claim 41.

89.   An organic light emitting device comprising the charge transporting material of claim 46.

90.   An organic light emitting device comprising the charge transporting material of claim 57.

91.   An organic light emitting device comprising the charge transporting material of claim 69.

92.   An organic light emitting device comprising the charge transporting material of claim 78.

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93.   A method for increasing the power efficiency of an organic light emitting device comprising incorporating in said device a charge transporting material according to claim 1.

94.   A method for increasing the efficiency of an organic light emitting device comprising incorporating in said device a electron transporting material according to claim 6.

95.   A method for increasing the efficiency of an organic light emitting device comprising incorporating in said device a hole transporting material according to claim 18.

96.   A method for increasing the efficiency of an organic light emitting device comprising incorporating in said device a charge transporting material according to claim 31.

97.   A method for increasing the efficiency of an organic light emitting device comprising incorporating in said device a charge transporting material according to claim 36.

98.   A method for increasing the efficiency of an organic light emitting device comprising incorporating in said device a charge transporting material according to claim 41.

99.   A method for increasing the efficiency of an organic light emitting device comprising incorporating in said device a charge transporting material according to claim 46.

100.   A method for increasing the efficiency of an organic light emitting device comprising incorporating in said device a charge transporting material according to claim 57.

101. A method for increasing the efficiency of an organic light emitting device comprising incorporating in said device a charge transporting material according to claim 69.

102. A method for increasing the efficiency of an organic light emitting device comprising incorporating in said device a charge transporting material according to claim 78.

INTERNATIONAL SEARCH REPORT

	International application No.
	PCT/US02/27202

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : H01B 1/00; H05B 33/00

US CL : 252/500, 501.1, 519.2, 519.21; 428/690, 917; 313/504, 506

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 252/500, 501.1, 519.2, 519.21; 428/690, 917; 313/504, 506; 257/102, 103

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,066,569 A (LIM) 03 January 1978 (03.01.1978), see the whole document, especially column 3, lines 9-17 and 23-29, and claims 4-7.	46-52, 56, 89 and 99
X	US 5,292,881 A (BERNETH et al) 08 March 1994 (08.03.1994), see the whole document, especially column 1, lines 7-9 and c. 3, l. 14 - c. 4, l. 36.	69-71
X	US 5,110,835 A (WALTER et al) 05 May 1992 (05.05.1992), see the abstract and column 3, lines 13-22.	69, 71, 72 and 75
X	US 4,618,453 A (KIM) 21 October 1986 (21.10.1986), see the whole document, especially column 3, lines 11-26 and claims 12 and 14.	1-3, 6, 11, 12, 15, 18, 23, 26, 36, 38 and 39
Y	US 6,350,534 B1 (BOERNER et al) 26 February 2002 (26.02.2002), see the whole document, especially column 3, line 27 - c. 4, l. 26.	1-102
Y	US 5,556,524 A (ALBERS) 17 September 1996 (17.09.1996), see the abstract, column 1, line 5 - c. 2, l. 21, c. 3, l. 4-17 and claims 7-9.	1-13, 15, 16, 18-23, 26, 27, 29, 30, 36, 38-40, 83-85, 87, 93-95 and 97
A	US 5,247,226 A (SATO et al) 21 September 1993 (21.09.1993), see the whole document.	1-102

☐ Further documents are listed in the continuation of Box C.	☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
		"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier application or patent published on or after the international filing date		
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2002 (30.10.2002)	06 DEC 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer DEBORAH THOMAS Marie R. Yamnitzky PARALEGAL SPECIALIST Telephone No. (703) 308-0661

Form PCT/ISA/210 (second sheet) (July 1998)

Continuation of B. FIELDS SEARCHED Item 3:

EAST/USPAT,US-PGPUB

search terms: charge, hole, electron, inject$5, transport$5, conduct$5, organometal$5, metal$2organic$1, metal$5, organ$3, chelat$5, complex$5, coordinat$5, ligand, conduct$5, electroconduct$5, improv$5, increas$5, metal$1ocene$1, naphthylimid$5, dinaphthylimid$5, binaphthylimid$5, naphthalimid$

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Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** METAL CHELATES

(57) **Abstract:** A photovoltaic device which uses a metal chelate as the photovoltaic element.

- 1 -

Metal Chelates

The present invention relates to photovoltaic devices and elements useful in such devices.

Photovoltaic devices, i.e. solar cells, are capable of converting solar radiation into useable electrical energy. The energy conversion occurs as a result of what is well known in the solar cell field as the photovoltaic effect. Solar radiation impinging on a solar cell and absorbed by an active region generates electrons and holes. The electrons and holes are separated by a built-in electric field, for example a rectifying junction, in the solar cell. This separation of electrons and holes results in the generation of an electrical current as explained below. For example, a built-in electric field can be generated in a solar cell by an active semiconductor layer with regions of P-type, intrinsic and N-type hydrogenated amorphous silicon. A built-in electric field can also be generated in a solar cell by, for example, a Schottky barrier. The electrons generated at the metal (Schottky barrier) semiconductor body junction flow towards the semiconductor body.

A typical simple photovoltaic solar cell comprises an electrically conductive substrate layer; a semiconductor body deposited upon said substrate layer and a transparent conductive layer over at least a portion of said semiconductor body for facilitating collection of electrical current produced by the photovoltaic cell.

The electrons generated in the intrinsic region, by absorption of solar radiation of the appropriate bandgap, produce electron-hole pairs. The separation of the electron-hole pairs with the electrons flowing toward the region of N-type conductivity, and the holes flowing toward the region of P-type conductivity, creates the photovoltage and photocurrent of the cell.

The photocurrent output of a solar cell is maximized by increasing the total number of photons of differing energy and wavelength which are absorbed by the

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semiconductor material. The solar spectrum roughly spans the region of wavelengths from about 300 nanometers to about 2200 nanometers, which corresponds to from about 4.2 eV to about 0.59 eV, respectively. The portion of the solar spectrum which is absorbed by the solar cell is determined by the size of the bandgap energy of the semiconductor material. In the past, solar cells were fabricated from single crystal materials such as gallium arsenide, which has a bandgap energy of about 1.45 eV, or crystalline silicon, C-Si, which has a bandgap energy of about 1.1 eV. Solar radiation having an energy less than the bandgap energy is not absorbed by the semiconductor material, and thus does not contribute to the generation of the photocurrent output of the cell.

Semiconductor materials such as GaAs and C-Si have been utilized together in solar cells to increase the overall conversion of solar energy into electrical energy. However, problems are encountered when different semiconductor materials are used in the same solar cell. One solution to the problem of fabricating a solar cell structure with different semiconductor materials was to use filters to reflect light of the appropriate wavelength onto a solar cell of the first material and transmit the non-absorbed light to a cell of the second semiconductor material. A second solution used semiconductor materials of differing bandgaps which could be epitaxially grown on one another, such as aluminum gallium arsenide, gallium arsenide, and gallium phosphide structures. Both these systems have been loosely called tandem junction solar cells. A third alternative was to stack individual solar cells of differing bandgap energies and connect the cells in series. These three alternatives are either cumbersome, expensive and/or bulky. A description of photovoltaic cells and their operation is disclosed in a paper by Jean-Michel Nunzi in C.R.Physique 3 (2002) 523-542.

We have found that a photovoltaic device can be made using metal chelates such as a rare earth or non rare earth metal chelate or a mixture of rare earth metal chelates as the photovoltaic element in place of the prior art semi conductors.

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Rare earth chelates are known which fluoresce in ultra violet radiation and A. P. Sinha (Spectroscopy of Inorganic Chemistry Vol. 2 Academic Press 1971) describes several classes of rare earth chelates with various monodentate and bidentate ligands.

Group III A metals and lanthanides and actinides with aromatic complexing agents have been described by G. Kallistratos (Chimica Chronika, New Series, 11, 249-266 (1982)). This reference specifically discloses the Eu(III), Tb(III), U(III) and U(IV) complexes of diphenyl-phosponamidotriphenyl-phosphoran.

EP 0556005A and 0744451A also disclose fluorescent chelates of transition or lanthanide or actinide metals.

Patent application WO98/58037 describes a range of lanthanide complexes which can be used in electroluminescent devices which have improved properties and give better results. Patent Applications PCT/GB98/01773, PCT/GB99/03619, PCT/GB99/04030, PCT/GB99/04024, PCT/GB99/04028, PCT/GB00/00268 describe electroluminescent complexes, structures and devices using rare earth chelates.

Hitherto such rare earth metal chelates have not been used in photovoltaic devices.

According to the invention there is provided a photovoltaic device comprising a metal chelate as the photovoltaic element.

The invention also provides a photovoltaic device which comprises sequentially (i) a first electrode comprising a metal, (ii) the photovoltaic element and (iii) a second electrode in which the photovoltaic element comprises a metal chelate.

By photovoltaic element is meant a compound which will generate electrons and holes when exposed to light.

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The metal chelates can absorb light of a specific wavelength or wavelengths depending on the metal and ligands used and, as the photocurrent output of a solar cell is maximized by increasing the total number of photons of differing energy and wavelength which are absorbed by the semiconductor material, by having a plurality of layers of different metal chelates which absorb light at different wavelengths, a wide range of the visible spectrum can be used. Metal chelates can also absorb light in the infra-red, ultra-violet or shorter wavelengths so improving the utilisation of sunlight and increasing the power achievable by a solar cell. Alternatively there can be several layers of metal chelates which absorb light in different parts of the spectrum.

The preferred metal chelates useful in the present invention have the formula

$$(L\alpha)_n M \text{ or } (L\alpha)_n \text{>} M \leftarrow Lp$$
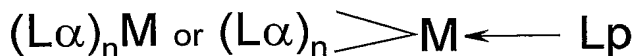
where $L\alpha$ and Lp are organic ligands, M is a metal and n is the valence state of the metal M and in which the ligands $L\alpha$ are the same or different.

There can be a plurality of ligands Lp which can be the same or different.

For example $(L_1)(L_2)(L_3)(L..)M$ (Lp) where M is a metal e.g. rare earth, transition metal, lanthanide or an actinide and $(L_1)(L_2)(L_3)(L...)$ are the same or different organic complexes and (Lp) is a neutral ligand. The total charge of the ligands $(L_1)(L_2)(L_3)(L..)$ is equal to the valence state of the metal M. Where there are 3 groups $L\alpha$ which corresponds to the III valence state of M the complex has the formula $(L_1)(L_2)(L_3)M$ (Lp) and the different groups $(L_1)(L_2)(L_3)$ may be the same or different.

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Lp can be monodentate, bidentate or polydentate and there can be one or more ligands Lp.

Preferably M is a metal ion having an unfilled inner shell and the preferred metals are selected from Sm(III), Eu(II), Eu(III), Tb(III), Dy(III), Yb(III), Lu(III), Gd (III), Gd(III) U(III), Tm(III), Ce (III), Pr(III), Nd(III), Pm(III), Dy(III), Ho(III), Er(III) and more preferably Eu(III), Tb(III), Dy(III), Gd (III).

Further compounds which can be used in the present invention are of general formula $(L\alpha)_n M_1 M_2$ where M_1 is the same as M above, M_2 is a non rare earth metal, $L\alpha$ is as above and n is the combined valence state of M_1 and M_2. The complex can also comprise one or more neutral ligands Lp so the complex has the general formula $(L\alpha)_n M_1 M_2 (Lp)$, where Lp is as above. The metal M_2 can be any metal which is not a rare earth, transition metal, lanthanide or an actinide; examples of metals which can be used include lithium, sodium, potassium, rubidium, caesium, beryllium, magnesium, calcium, strontium, barium, copper (I), copper (II), silver, gold, zinc, cadmium, boron, aluminium, gallium, indium, germanium, tin (II), tin (IV), antimony (II), antimony (IV), lead (II), lead (IV) and metals of the first, second and third groups of transition metals in different valence states e.g. manganese, iron, ruthenium, osmium, cobalt, nickel, palladium(II), palladium(IV), platinum(II), platinum(IV), cadmium, chromium. titanium, vanadium, zirconium, tantulum, molybdenum, rhodium, iridium, titanium, niobium, scandium, yttrium.

For example $(L_1)(L_2)(L_3)(L..)M (Lp)$ where M is a rare earth, transition metal, lanthanide or an actinide and $(L_1)(L_2)(L_3)(L...)$ and (Lp) are the same or different organic complexes.

Further organometallic complexes which can be used in the present invention are binuclear, trinuclear and polynuclear organometallic complexes e.g. of formula

$(Lm)_x M_1 \leftarrow M_2(Ln)_y$ e.g.

- 6 -
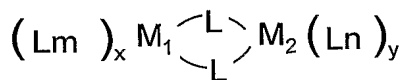
$$\left(Lm \right)_x M_1 \genfrac{}{}{0pt}{}{\diagup L \diagdown}{\diagdown L \diagup} M_2 \left(Ln \right)_y$$

where L is a bridging ligand and where M_1 is a rare earth metal and M_2 is M_1 or a non rare earth metal, Lm and Ln are the same or different organic ligands $L\alpha$ as defined above, x is the valence state of M_1 and y is the valence state of M_2.

In these complexes there can be a metal to metal bond or there can be one or more bridging ligands between M_1 and M_2 and the groups Lm and Ln can be the same or different.

By trinuclear is meant there are three rare earth metals joined by a metal to metal bond i.e. of formula
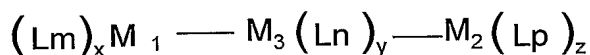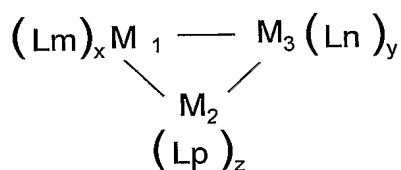
$$\left(Lm \right)_x M_1 \text{———} M_3 \left(Ln \right)_y \text{——} M_2 \left(Lp \right)_z$$

or

$$\left(Lm \right)_x M_1 \text{———} M_3 \left(Ln \right)_y$$
$$\diagdown \quad \diagup$$
$$M_2$$
$$\left(Lp \right)_z$$

where M_1, M_2 and M_3 are the same or different rare earth metals and Lm, Ln and Lp are organic ligands, $L\alpha$ and x is the valence state of M_1, y is the valence state of M_2 and z is the valence state of M_3. Lp can be the same as Lm and Ln or different.

The rare earth metals and the non rare earth metals can be joined together by a metal to metal bond and/or via an intermediate bridging atom, ligand or molecular group.

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For example the metals can be linked by bridging ligands e.g.

$$\left(Lm\right)_x M_1 \begin{array}{c} \overset{L}{\frown} \\ \underset{L}{\smile} \end{array} M_3 \left(Ln\right)_y \begin{array}{c} \overset{L}{\frown} \\ \underset{L}{\smile} \end{array} M_2 \left(Lp\right)_z$$
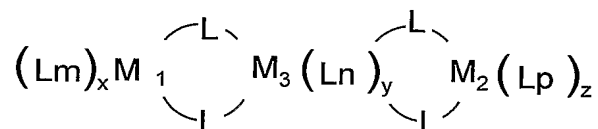
or
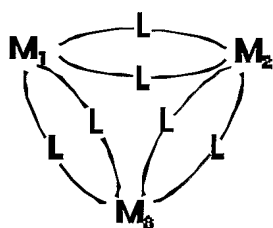
where L is a bridging ligand

By polynuclear is meant there are more than three metals joined by metal to metal bonds and/or via intermediate ligands

$$M_1 \longrightarrow M_2 \longrightarrow M_3 \longrightarrow M_4$$

or

$$M_1 \longrightarrow M_2 \longrightarrow M_4 \longrightarrow M_3$$

or
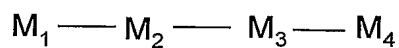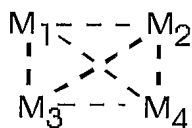
or

- 8 -
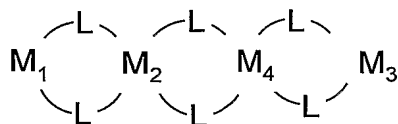
where M_1, M_2, M_3 and M_4 are rare earth metals and L is a bridging ligand.

The metal M_2 can be any metal which is not a rare earth, transition metal, lanthanide or an actinide examples of metals which can be used include lithium, sodium, potassium, rubidium, caesium, beryllium, magnesium, calcium, strontium, barium, copper, silver, gold, zinc, cadmium, boron, aluminium, gallium, indium, germanium, tin, antimony, lead, and metals of the first, second and third groups of transition metals e.g. manganese, iron, ruthenium, osmium, cobalt, nickel, palladium, platinum, cadmium, chromium. titanium, vanadium, zirconium, tantulum, molybdenum, rhodium, iridium, titanium, niobium, scandium, yttrium etc.

Preferably $L\alpha$ is selected from β diketones such as those of formulae
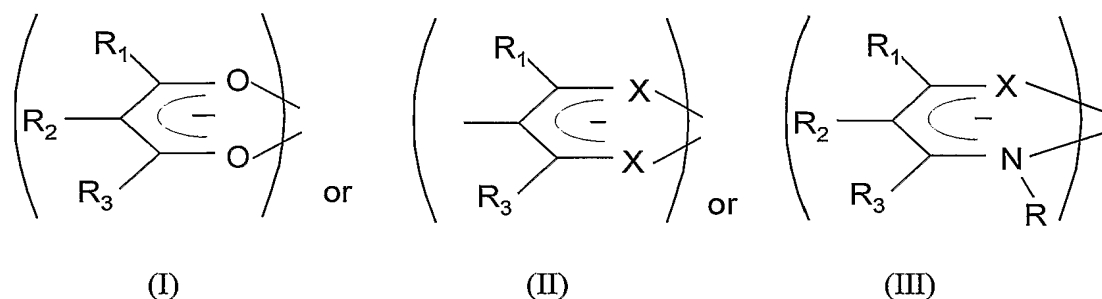
(I)   (II)   (III)

where R_1, R_2 and R_3 can be the same or different and are selected from hydrogen, and substituted and unsubstituted hydrocarbyl groups such as substituted and unsubstituted aliphatic groups, substituted and unsubstituted aromatic, heterocyclic and polycyclic ring structures, fluorocarbons such as trifluoryl methyl groups, halogens such as fluorine or thiophenyl groups; R_1, R_2 and R_3 can also form substituted and unsubstituted fused aromatic, heterocyclic and polycyclic ring structures and can be copolymerisable with a monomer e.g. styrene. X is Se, S or O, Y can be hydrogen, substituted or unsubstituted hydrocarbyl groups, such as substituted and unsubstituted aromatic, heterocyclic and polycyclic ring structures,

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fluorine, fluorocarbons such as trifluoryl methyl groups, halogens such as fluorine or thiophenyl groups or nitrile.

Examples of R_1 and/or R_2 and/or R_3 include aliphatic, aromatic and heterocyclic alkoxy, aryloxy and carboxy groups, substituted and substituted phenyl, fluorophenyl, biphenyl, phenanthrene, anthracene, naphthyl and fluorene groups alkyl groups such as t-butyl, heterocyclic groups such as carbazole.

Some of the different groups $L\alpha$ may also be the same or different charged groups such as carboxylate groups so that the group L_1 can be as defined above and the groups L_2, $L_3...$ can be charged groups such as

(IV)
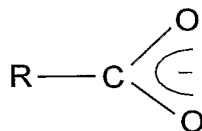
where R is R_1 as defined above or the groups L_1, L_2 can be as defined above and $L_3...$ etc. are other charged groups.

R_1, R_2 and R_3 can also be

       where X is O, S, Se or NH.

(V)

A preferred moiety R_1 is trifluoromethyl CF_3 and examples of such diketones are, banzoyltrifluoroacetone, p-chlorobenzoyltrifluoroacetone, p-bromotrifluoroacetone, p-phenyltrifluoroacetone, 1-naphthoyltrifluoroacetone, 2-naphthoyltrifluoroacetone, 2-phenathoyltrifluoroacetone, 3-phenanthoyltrifluoroacetone, 9-anthroyltrifluoroacetonetrifluoroacetone, cinnamoyltrifluoroacetone, and 2-thenoyltrifluoroacetone.

The different groups Lα may be the same or different ligands of formulae
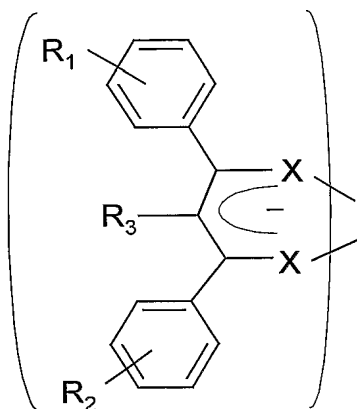
5   (VI)

where X is O, S, or Se and R_1 R_2 and R_3 are as above.

The different groups Lα may be the same or different quinolate derivatives such as

or
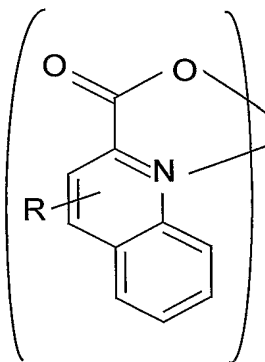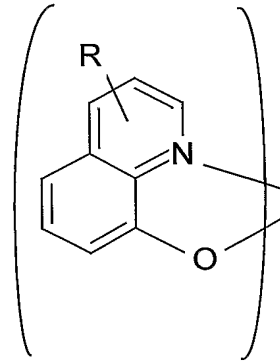
(VII)   (VIII)

10   where R is hydrocarbyl, aliphatic, aromatic or heterocyclic carboxy, aryloxy, hydroxy
or alkoxy e.g. the 8 hydroxy quinolate derivatives or

or
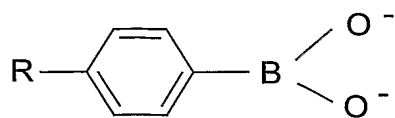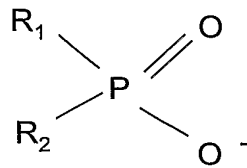
(IX)   (X)

- 11 -

where R, R_1, and R_2 are as above or are H or F e.g. R_1 and R_2 are alkyl or alkoxy groups
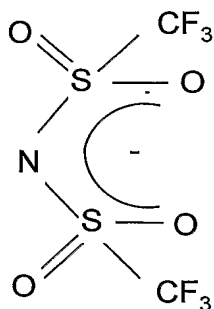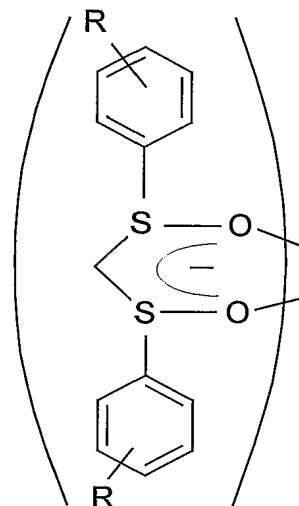
(XI)   (XII)

5   As stated above the different groups Lα may also be the same or different carboxylate groups e.g.
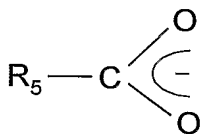
(XIII)

where R_5 is a substituted or unsubstituted aromatic, polycyclic or heterocyclic ring a

10   polypyridyl group, R_5 can also be a 2-ethyl hexyl group so L_n is 2-ethylhexanoate or R_5 can be a chair structure so that L_n is 2-acetyl cyclohexanoate or Lα can be
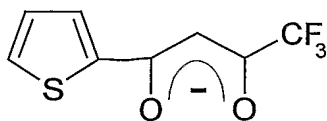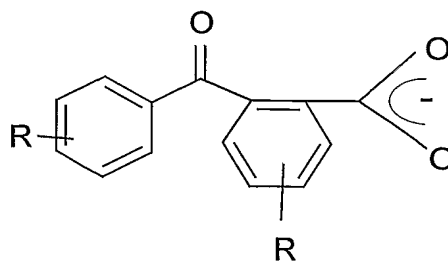
(XIV)   (XIVa)

where R is as above e.g. alkyl, allenyl, amino or a fused ring such as a cyclic or polycyclic ring.

The different groups $L\alpha$ may also be

(XV)

or

(XVI)
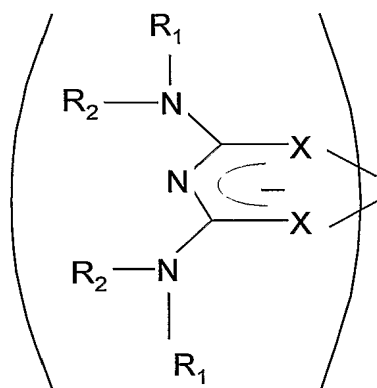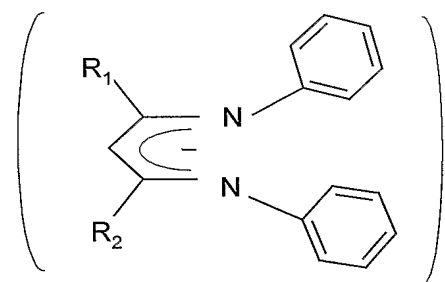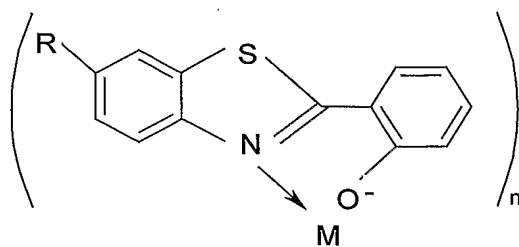
(XVII)

or
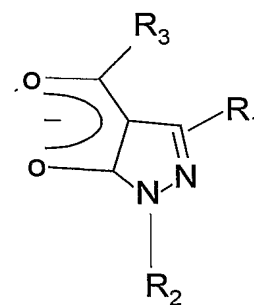
(XVIIa)

Where R, R_1 and R_2 are as above.

The groups L_P can be selected from

- 13 -

$$O = P \underset{\underset{Ph}{|}}{\overset{\overset{Ph}{|}}{}} - N = P \underset{\underset{Ph}{|}}{\overset{\overset{Ph}{|}}{}} - Ph$$
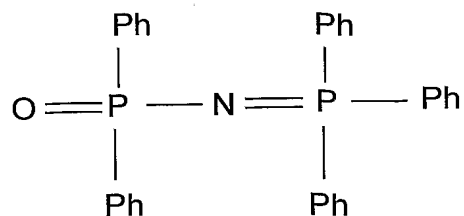
(XVIII)

where each Ph which can be the same or different and can be a phenyl (OPNP) or a substituted phenyl group, other substituted or unsubstituted aromatic group, a substituted or unsubstituted heterocyclic or polycyclic group, a substituted or unsubstituted fused aromatic group such as a naphthyl, anthracene, phenanthrene or pyrene group. The substituents can be for example an alkyl, aralkyl, alkoxy, aromatic, heterocyclic, polycyclic group, halogen such as fluorine, cyano, amino. Substituted amino etc. Examples are given in figs. 1 and 2 of the drawings where R, R_1, R_2, R_3 and R_4 can be the same or different and are selected from hydrogen, hydrocarbyl groups, substituted and unsubstituted aromatic, heterocyclic and polycyclic ring structures, fluorocarbons such as trifluoryl methyl groups, halogens such as fluorine or thiophenyl groups; R, R_1, R_2, R_3 and R_4 can also form substituted and unsubstituted fused aromatic, heterocyclic and polycyclic ring structures and can be copolymerisable with a monomer e.g. styrene. R, R_1, R_2, R_3 and R_4 can also be unsaturated alkylene groups such as vinyl groups or groups

$$- C - CH_2 = CH_2 - R$$
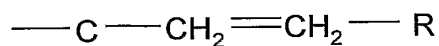
where R is as above.

L_p can also be compounds of formulae

– 14 –

(XVIV)   or   (XVIVa)   or   (XX)   or   (XXI)
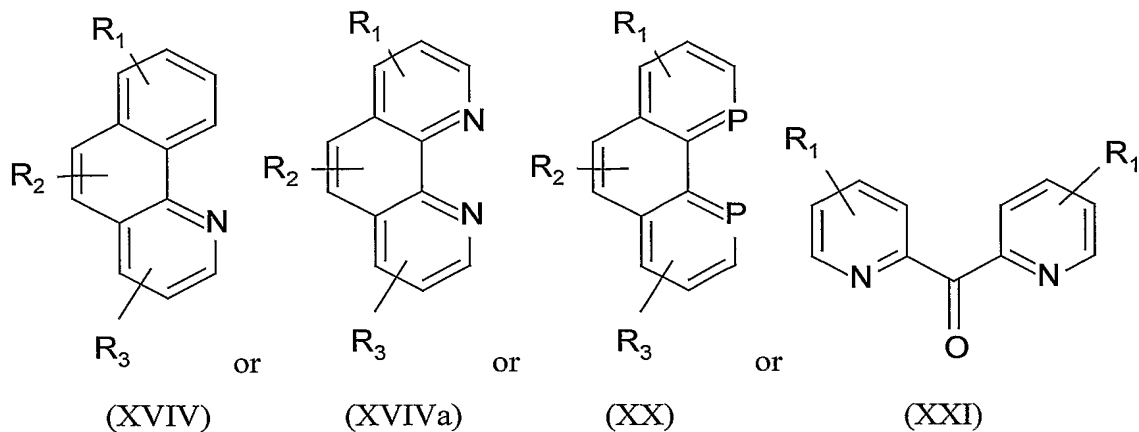
where R_1, R_2 and R_3 are as referred to above, for example bathophen shown in fig. 3 of the drawings in which R is as above or

5

(XXII)   (XXIII)
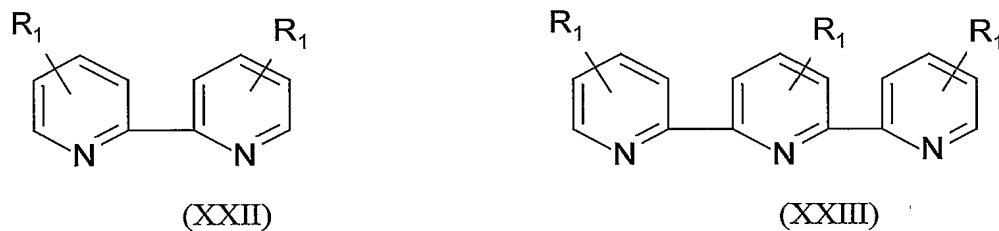
where R_1, R_2 and R_3 are as referred to above.

10

L_p can also be

(XXIV)   or   (XXV)
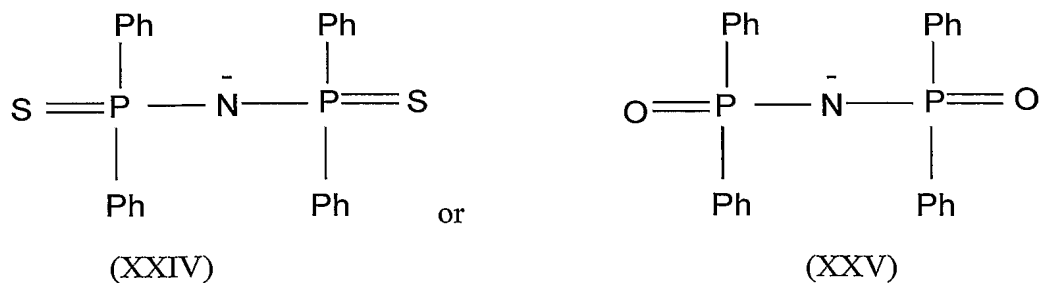
15   where Ph is as above.

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Other examples of L_p chelates are as shown in figs. 4 and fluorene and fluorene derivatives e.g. a shown in figs. 5 and compounds of formulae as shown as shown in figs. 6 to 8.

5   Specific examples of $L\alpha$ and Lp are tripyridyl and TMHD, and TMHD complexes, $\alpha, \alpha', \alpha''$ tripyridyl, crown ethers, cyclans, cryptans phthalocyanans, porphoryins ethylene diamine tetramine (EDTA), DCTA, DTPA and TTHA, where TMHD is 2,2,6,6-tetramethyl-3,5-heptanedionato and OPNP is diphenylphosphonimide triphenyl phosphorane. The formulae of the polyamines are shown in fig. 9.

10

Other electroluminescent materials which can be used include metal quinolates such as lithium quinolate, aluminium quinolate, scandium quinolate zirconium quinolate, hafnium quinolate vanadium quinolate etc. The quinolates can be doped e.g. with a dye such as diphenylquinacridine, diphenylquinacridone, coumarins, perylene and

15   their derivatives.

Other electroluminescent materials which can be used include organic complexes of non rare earth metals such as lithium, sodium, potassium, rubidium, caesium, beryllium, magnesium, calcium, strontium, barium, copper, silver, gold, zinc,

20   cadmium, boron, aluminium, gallium, indium, germanium, tin, antimony, lead, and metals of the first, second and third groups of transition metals e.g. manganese, iron, ruthenium, osmium, cobalt, nickel, palladium, platinum, cadmium, chromium. titanium, vanadium, zirconium, tantulum, molybdenum, rhodium, iridium, titanium, niobium, scandium, yttrium etc. which emit light when an electric current is passed

25   through it. The complexes can be formed with the ligands of formula (I) to (XVII) above, optionally with a neutral ligand of formula L_p as defined above.

Such complexes are complexes of β-diketones e.g. tris -(1,3-diphenyl-1-3-propanedione) (DBM) and suitable metal complexes are Al(DBM)$_3$, Zn(DBM)$_2$ and

30   Mg(DBM)$_2$, Sc(DBM)$_3$ etc.

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Further complexes which can be used as the photovoltaic element are borate complexes of formula
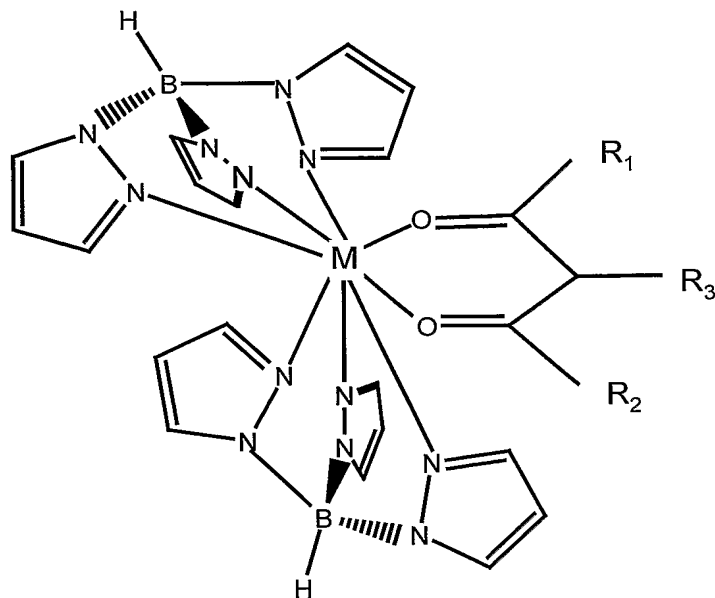
where M is a rare earth, lanthanide or an actinide and R_1, R_2 and R_3 are as defined above.

A photovoltaic device can be made in the conventional way for example by forming a layer of the metal chelate on a metal so the metal forms a first electrode and preferably the other, second electrode, comprises a transparent conductive layer. This electrode is preferably a transparent substrate which is a conductive glass or plastic material which acts as the cathode; preferred substrates are conductive glasses such as indium tin oxide coated glass, but any glass which is conductive or has a conductive layer can be used, so that, when light falls on the metal chelate an electric field is generated between the electrodes.

There are a very large number of designs for photovoltaic devices and solar cells and a survey of such devices is given in the Jean-Michel Nunzi Article referred to above and in the references thereto. In general the metal chelates can be used as the photovoltaic element in such devices.

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The metal chelate material can be deposited on the metal or conductive transparent material substrate directly by evaporation from a solution of the material in an organic solvent. The solvent which is used will depend on the material, but chlorinated hydrocarbons such as dichloromethane, n-methyl pyrrolidone, dimethyl sulphoxide, tetra hydrofuran dimethylformamide etc. are suitable in many cases.

Alternatively the material can be deposited by spin coating from solution or by vacuum deposition from the solid state e.g. by sputtering or any other conventional method can be used.

As stated above, the electrons by absorption of solar radiation of the appropriate bandgap, produce electron-hole pairs. The separation of the electron-hole pairs with the electrons flowing toward the region of N-type conductivity, and the holes flowing toward the region of P-type conductivity, creates the photovoltage and photocurrent of the cell. By having a layer of a hole transmitting material, i.e. a p-type transmitter between the cathode and the metal chelate and/or a layer of an electron transmitting material between the metal chelate and the anode, increased mobility of the holes and the electrons can be achieved increasing the effectiveness of the photovoltaic cell.

Hole transmitting layers are used in polymer electroluminescent devices and any of the known hole transmitting materials in film form can be used.

The hole transporting material can be an amine complex such as   poly (vinylcarbazole), N, N'-diphenyl-N, N'-bis (3-methylphenyl) -1,1' -biphenyl -4,4'-diamine (TPD), an unsubstituted or substituted polymer of an amino substituted aromatic compound, a polyaniline, substituted polyanilines, polythiophenes, substituted polythiophenes, polysilanes etc. Examples of polyanilines are polymers of

- 18 -
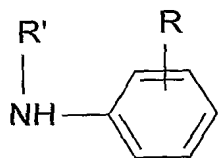
(XXVI)

where R is in the ortho – or meta-position and is hydrogen, C1-18 alkyl, C1-6 alkoxy, amino, chloro, bromo, hydroxy or the group
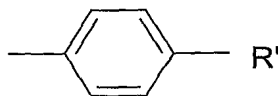
where R is alky or aryl and R' is hydrogen, C1-6 alkyl or aryl with at least one other monomer of formula I above.

Or the hole transporting material can be a polyaniline. Polyanilines which can be used in the present invention have the general formula
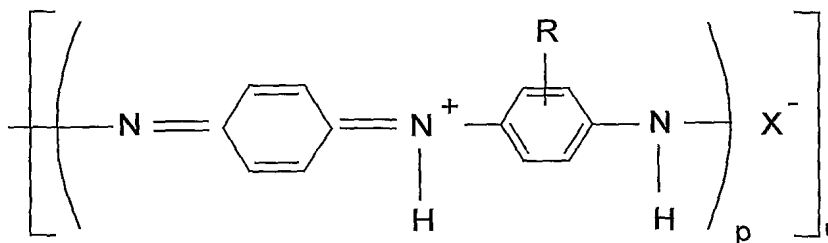
(XXVII)

where p is from 1 to 10 and n is from 1 to 20, R is as defined above and X is an anion, preferably selected from Cl, Br, SO_4, BF_4, PF_6, H_2PO_3, H_2PO_4, arylsulphonate, arenedicarboxylate, polystyrenesulphonate, polyacrylate alkysulphonate, vinylsulphonate, vinylbenzene sulphonate, cellulose sulphonate, camphor sulphonates, cellulose sulphate or a perfluorinated polyanion.

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Examples of arylsulphonates are p-toluenesulphonate, benzenesulphonate, 9,10-anthraquinone-sulphonate and anthracenesulphonate; an example of an arenedicarboxylate is phthalate and an example of arenecarboxylate is benzoate.

We have found that protonated polymers of the unsubstituted or substituted polymer of an amino substituted aromatic compound such as a polyaniline are difficult to evaporate or cannot be evaporated, however we have surprisingly found that if the unsubstituted or substituted polymer of an amino substituted aromatic compound is deprotonated then it can be easily evaporated i.e. the polymer is evaporable.

Preferably evaporable deprotonated polymers of unsubstituted or substituted polymer of an amino substituted aromatic compound are used. The de-protonated unsubstituted or substituted polymer of an amino substituted aromatic compound can be formed by deprotonating the polymer by treatment with an alkali such as ammonium hydroxide or an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide.

The degree of protonation can be controlled by forming a protonated polyaniline and de-protonating. Methods of preparing polyanilines are described in the article by A. G. MacDiarmid and A. F. Epstein, Faraday Discussions, Chem Soc.88 P319 1989.

The conductivity of the polyaniline is dependant on the degree of protonation with the maximum conductivity being when the degree of protonation is between 40 and 60% e.g. about 50%.

Preferably the polymer is substantially fully deprotonated.

A polyaniline can be formed of octamer units i.e. p is four e.g.
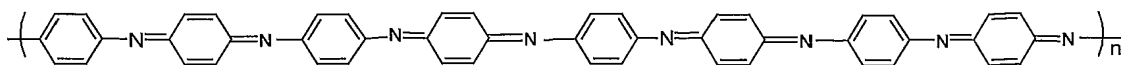
The polyanilines can have conductivities of the order of 1×10^{-1} Siemen cm^{-1} or higher.

The aromatic rings can be unsubstituted or substituted e.g. by a C1 to 20 alkyl group such as ethyl.

The polyaniline can be a copolymer of aniline and preferred copolymers are the copolymers of aniline with o-anisidine, m-sulphanilic acid or o-aminophenol, or o-toluidine with o-aminophenol, o-ethylaniline, o-phenylene diamine or with amino anthracenes.

Other polymers of an amino substituted aromatic compound which can be used include substituted or unsubstituted polyaminonapthalenes, polyaminoanthracenes, polyaminophenanthrenes, etc. and polymers of any other condensed polyaromatic compound. Polyaminoanthracenes and methods of making them are disclosed in US Patent 6,153,726. The aromatic rings can be unsubstituted or substituted e.g. by a group R as defined above.

Other hole transporting materials are conjugated polymer and the conjugated polymers which can be used can be any of the conjugated polymers disclosed or referred to in US 5807627, PCT/WO90/13148 and PCT/WO92/03490.

The preferred conjugated polymers are poly (p-phenylenevinylene)-PPV and copolymers including PPV. Other preferred polymers are poly(2,5 dialkoxyphenylene vinylene) such as poly (2-methoxy-5-(2-methoxypentyloxy-1,4-phenylene vinylene), poly(2-methoxypentyloxy)-1,4-phenylenevinylene), poly(2-methoxy-5-(2-dodecyloxy-1,4-phenylenevinylene) and other poly(2,5 dialkoxyphenylenevinylenes)

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with at least one of the alkoxy groups being a long chain solubilising alkoxy group, polyfluorenes and oligofluorenes, polyphenylenes and oligophenylenes, polyanthracenes and oligo anthracenes, ploythiophenes and oligothiophenes.

5   In PPV the phenylene ring may optionally carry one or more substituents e.g. each independently selected from alkyl, preferably methyl, alkoxy, preferably methoxy or ethoxy.

10   Any poly(arylenevinylene) including substituted derivatives thereof can be used and the phenylene ring in poly(p-phenylenevinylene) may be replaced by a fused ring system such as anthracene or naphthlyene ring and the number of vinylene groups in each polyphenylenevinylene moiety can be increased e.g. up to 7 or higher.

15   The conjugated polymers can be made by the methods disclosed in US 5807627, PCT/WO90/13148 and PCT/WO92/03490.

The thickness of the hole transporting layer is preferably 20nm to 200nm.

20   The polymers of an amino substituted aromatic compound such as polyanilines referred to above can also be used as buffer layers with or in conjunction with other hole transporting materials.

25   The structural formulae of some other hole transporting materials are shown in Figures 12, 13, 14, 15 and 16 of the drawings, where R_1, R_2 and R_3 can be the same or different and are selected from hydrogen, and substituted and unsubstituted hydrocarbyl groups such as substituted and unsubstituted aliphatic groups, substituted and unsubstituted aromatic, heterocyclic and polycyclic ring structures, fluorocarbons such as trifluoryl methyl groups, halogens such as fluorine or thiophenyl groups; R_1, R_2 and R_3 can also form substituted and unsubstituted fused aromatic, heterocyclic

30   and polycyclic ring structures and can be copolymerisable with a monomer e.g.

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styrene. X is Se, S or O, Y can be hydrogen, substituted or unsubstituted hydrocarbyl groups, such as substituted and unsubstituted aromatic, heterocyclic and polycyclic ring structures, fluorine, fluorocarbons such as trifluoryl methyl groups, halogens such as fluorine or thiophenyl groups or nitrile.

Examples of R_1 and/or R_2 and/or R_3 include aliphatic, aromatic and heterocyclic alkoxy, aryloxy and carboxy groups, substituted and substituted phenyl, fluorophenyl, biphenyl, phenanthrene, anthracene, naphthyl and fluorene groups alkyl groups such as t-butyl, heterocyclic groups such as carbazole.

Optionally there is a layer of an electron injecting material between the anode and the electroluminescent material layer; the electron injecting material is a material which will transport electrons when an electric current is passed through it; electron injecting materials include a metal complex such as a metal quinolate e.g. an aluminium quinolate, lithium quinolate, a cyano anthracene such as 9,10 dicyano anthracene, cyano substituted aromatic compounds, tetracyanoquinidodimethane a polystyrene sulphonate or a compound with the structural formulae shown in figures 9 or 10 of the drawings in which the phenyl rings can be substituted with substituents R as defined above.

The cathode is preferably a transparent substrate such as a conductive glass or plastic material which acts as the anode. Preferred substrates are conductive glasses such as indium tin oxide coated glass, but any glass which is conductive or has a conductive layer such as a metal or conductive polymer can be used. Conductive polymers and conductive polymer coated glass or plastics materials can also be used as the substrate.

The anode is preferably a low work function metal e.g. aluminium, calcium, lithium, silver/magnesium alloys, rare earth metal alloys etc., aluminium is a preferred metal.

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A metal fluoride such as an alkali metal, rare earth metal or their alloys can be used as the second electrode for example by having a metal fluoride layer formed on a metal.

5   As stated above, the photocurrent output of a solar cell is maximized by increasing the total number of photons of differing energy and wavelength which are absorbed by the semiconductor material and it is a feature of the present invention that the rare earth metal chelates can absorb light of a specific wavelength depending on the metal and ligands used so, by having a plurality of layers of different metal chelates of
10   differing bandgaps which absorb light at different wavelengths, a wide range of the visible spectrum can be used. Metal chelates can be also used which will absorb light in the infra-red, ultra-violet or shorter wavelengths so improving the utilisation of sunlight and increasing the power achievable by a solar cell.

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20   differing bandgaps which absorb light at different wavelengths, a wide range of the visible spectrum can be used. Metal chelates can be also used which will absorb light in the infra-red, ultra-violet or shorter wavelengths so improving the utilisation of sunlight and increasing the power achievable by a solar cell.

25   Alternatively individual solar cells of differing bandgap energies i.e. using different metal chelates of differing bandgaps which absorb light at different wavelengths can be connected in series.

Devices of the invention are illustrated in the drawings in which:-

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Fig. 17 shows a simple photovoltaic cell

Figs. 18 and 19 show other cells and

Fig. 20 shows a tandem cell

5

Referring to fig. 17 a simple cell comprises a metal anode e.g. made of aluminium (1) a layer of an electroluminescent material (2) as described herein and a cathode comprising an indium titanium oxide (ITO) coated glass (3). When light passes through the ITO coated glass it is absorbed by the electroluminescent material layer (2), which is the photovoltaic element, and an electric field is generated between the anode and cathode and when the anode and cathode are connected through an electric circuit an electric current will flow between them.

Referring to fig. 18 there is a layer of an electron transmitting material (4) between the layers (2) and (1).

Referring to fig. 19 there is a layer of a hole transporting layer (5) between the layers (2) and (3).

Referring to fig. 20 this shows a tandem solar cell in which there are a plurality of cells in series of fig. 17 formed of a cathode (11), an electroluminescent layer (13) and anode (12) so that a larger field is generated between the end anode and cathode, in order for there to be a transmission of light through the cells the anodes and cathodes of the intermediate cells are transparent. At least some of the photovoltaic elements (13) in each of the cells are different to adsorb light at a range of wavelengths.

Example 1

A photovoltaic device was fabricated on a clean and dried ITO coated glass piece (1 x 1cm^2) by sequentially forming layers by vacuum evaporation to form a structure

ITO/CuPc(20nm)/TPD(50nm)/ Eu (DBM)$_3$(OPNP)/(85nm)Alq$_3$/LiF(0.4nm)/Al

Where CuPc is copper phthalocyanine, TPD is N, N'-diphenyl-N, N'-bis (3-methylphenyl) -1,1' -biphenyl -4,4'-diamine, Alq$_3$ is aluminium quinolate, LiF is lithium fluoride and Al is aluminium.

To deposit the layers the organic coating on the portion which had been etched with the concentrated hydrochloric acid was wiped with a cotton bud. The coated electrodes were stored in a vacuum desiccator over a molecular sieve and phosphorous pentoxide until they were loaded into a vacuum coater (Edwards, 10^{-6} torr) and aluminium top contacts made. The active area of the photovoltaic device was 0.08 cm by 0.1 cm^2 the devices were then kept in a vacuum desiccator until the photovoltaic studies were performed.

The device was connected in an electric circuit and exposed to light of various wavelengths λ and the voltage and current measured the results are shown graphically in fig. 21 where the open circuit voltage Voc and short circuit current Jsc (as described in the Jean-Michel Nunzi Article referred to above) were obtained. The white light was obtained from a simulated daylight fluorescent bulb.

Example 2

Example 1 was repeated using a structure comprising

ITO/CuPc(20nm)/α-NPB(75nm)/Zrq$_4$:DPQA(75:0.75nm)/Zrq$_4$10nm)Alq$_3$/LiF(0.4nm/Al

Where α-NPB is as shown in fig. 16a, DPQA is diphenylquinacridone.

The Zrq$_4$ is zirconium quinolate and the Zrq$_4$:DPQA layer was formed by concurrent vacuum deposition to form a zirconium quinolate layer doped with DPQA. The weight ratio of the Zrq$_4$ and DPQA is conveniently shown by a relative thickness measurement.

The device was connected in an electric circuit and exposed to light of various wavelengths λ and the voltage and current measured the results are shown graphically in fig. 22 where the open circuit voltage Voc and short circuit current Jsc (as described in the Jean-Michel Nunzi Article referred to above) were obtained. The white light was obtained from a simulated daylight fluorescent bulb.

Example 3

Example 1 was repeated using a structure comprising

ITO/CuPc(20nm)/α-NPB(75nm)/Liq(65nm/Al.

Where Liq is lithium quinolate

The device was connected in an electric circuit and exposed to light of various wavelengths λ and the voltage and current measured the results are shown graphically in fig. 23 where the open circuit voltage Voc and short circuit current Jsc (as described in the Jean-Michel Nunzi Article referred to above) were obtained. The white light was obtained from a simulated daylight fluorescent bulb.

Example 4

Example 1 was repeated using a structure comprising

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ITO/CuPc(20nm)/α-NPB(75nm)/Liq(65nm)LiF(0.4nm/Al.

The device was connected in an electric circuit and exposed to light of various wavelengths λ and the voltage and current measured the results are shown graphically in fig. 24 where the open circuit voltage Voc and short circuit current Jsc (as described in the Jean-Michel Nunzi Article referred to above) were obtained. The white light was obtained from a simulated daylight fluorescent bulb.

Example 5

Devices were made as in Example 1 of structure

ITO/CuPc(25)/α-NPB(80)/CBP:Compound A(30:2)/BCP(10)/Zrq$_4$(60)/LiF(0.2)/Al

Where the film thicknesses are in nanometres and CBP is as in fig. 4b and BCP is bathocupron

compound A was
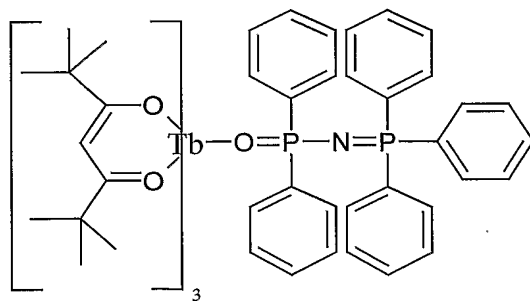
Similar devices were made with compounds B and C in place of compound A where compound B is
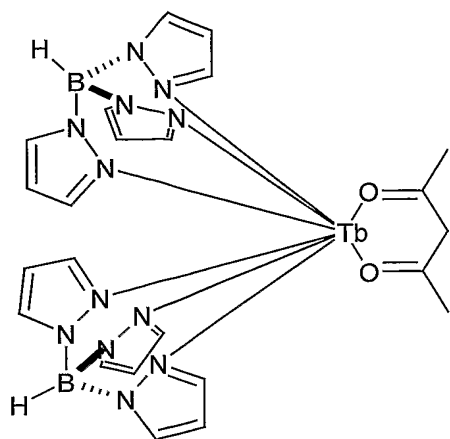
and compound C is
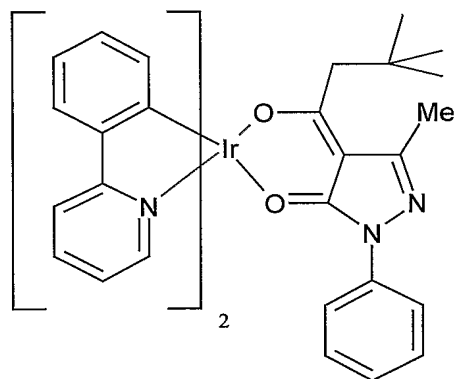
5

The results are shown in the Table

Table

Photovoltaic element	V^{OC}_{Ph} / mV	J^{SC}_{Ph} / mA cm^{-2}	λ / nm
A	7.5	- 0.4	600
B	-0.3	2.2	500
C	-159	0.4	550

10

Claims

1. A photovoltaic device comprising a metal chelate as the photovoltaic element.

5   2. A photovoltaic device as claimed in claim 1 which comprises sequentially (i) a first electrode comprising a metal, (ii) the photovoltaic element and (iii) a second electrode.

3. A device as claimed in claim 1 or 2 in which the photovoltaic element comprises
10   an organo metallic complex of formula

$$(L\alpha)_n M \text{ or } (L\alpha)_n \!\!>\!\! M \longleftarrow Lp$$
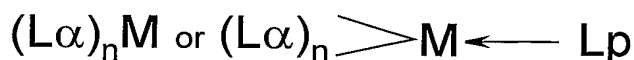
where $L\alpha$ and Lp are organic ligands, M is a metal and n is the valence state of the
15   metal M and in which the ligands $L\alpha$ are the same or different.

4. A device as claimed in any one of claims 1 to 4 in which the metal M is a rare earth, transition metal, lanthanide or an actinide.

20   5. A device as claimed in claim 4 in which the said rare earth, transition metal, lanthanide or an actinide is selected from Sm(III), Eu(II), Eu(III), Tb(III), Dy(III), Yb(III), Lu(III), Gd (III), Gd(III) U(III), Tm(III), Ce (III), Pr(III), Nd(III), Pm(III), Dy(III), Ho(III) and Er(III).

25   6. A device as claimed in any one of claims 1 to 3 in which the metal M is a non rare earth metal.

7. A device as claimed in claim 6 in which the metal M is selected from lithium, sodium, potassium, rubidium, caesium, beryllium, magnesium, calcium, strontium,

barium, copper, silver, gold, zinc, cadmium, boron, aluminium, gallium, indium, germanium, tin, antimony, lead, and metals of the first, second and third groups of transition metals, manganese, iron, ruthenium, osmium, cobalt, nickel, palladium, platinum, cadmium, chromium. titanium, vanadium, zirconium, tantulum, molybdenum, rhodium, iridium, titanium, niobium, scandium and yttrium.

8. A device as claimed in any one of claims 3 to 7 in which there are a plurality of ligands Lp which can be the same or different.

9. A device as claimed in any one of the preceding claims in which the photovoltaic element comprises an organo metallic complex of formula $(L_n)_n M_1 M_2$ or $(L_n)_n M_1 M_2 (L_p)$, where L_n is $L\alpha$, L_p is a neutral ligand M_1 is a rare earth, transition metal, lanthanide or an actinide, M_2 is a non rare earth metal and n is the combined valence state of M_1 and M_2.

10. A device as claimed in any one of the preceding claims in which the photovoltaic element comprises a binuclear, trinuclear or polynuclear organometallic complex of formula
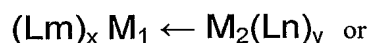
$$(Lm)_x M_1 \leftarrow M_2(Ln)_y \quad \text{or}$$

$$\left(Lm \right)_x M_1 \overset{\frown{L}}{\underset{\smallsmile{L}}{\Big\rangle}} M_2 \left(Ln \right)_y$$

where L is a bridging ligand and where M_1 is a rare earth metal and M_2 is M_1 or a non rare earth metal, Lm and Ln are the same or different organic ligands $L\alpha$ as defined above, x is the valence state of M_1 and y is the valence state of M_2 or
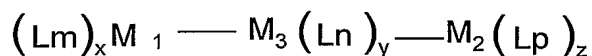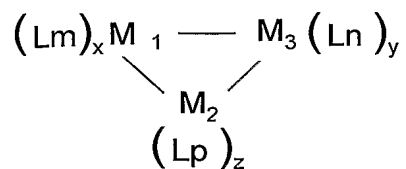
$$(Lm)_x M_1 \text{———} M_3 \left(Ln \right)_y \text{———} M_2 \left(Lp \right)_z$$

or

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$$\left(Lm \right)_x M_1 \longrightarrow M_3 \left(Ln \right)_y$$
$$\backslash \quad M_2 \quad /$$
$$\left(Lp \right)_z$$

where M_1, M_2 and M_3 are the same or different rare earth metals and Lm, Ln and Lp

are organic ligands Lα and x is the valence state of M_1, y is the valence state of M_2

and z is the valence state of M_3 and Lp can be the same as Lm and Ln or different or

$$\left(Lm \right)_x M_1 \quad {}^{L}_{L} \quad M_3 \left(Ln \right)_y \quad {}^{L}_{L} \quad M_2 \left(Lp \right)_z$$

or

$$M_1 \quad {}^{L}_{L} \quad M_2$$
$$L \quad L$$
$$L \quad L$$
$$M_3$$

or

$$M_1 \longrightarrow M_2 \longrightarrow M_3 \longrightarrow M_4$$

or

$$M_1 \longrightarrow M_2 \longrightarrow M_4 \longrightarrow M_3$$

or

- 32 -

$$M_1 - - - M_2$$
$$M_3 - - - M_4$$

or

$$M_1 \quad M_2 \quad M_4 \quad M_3$$
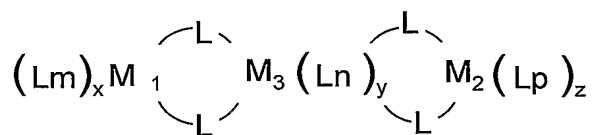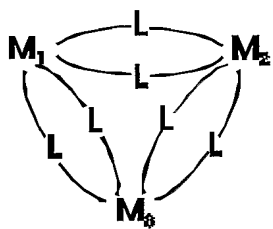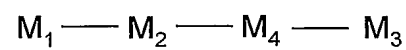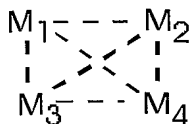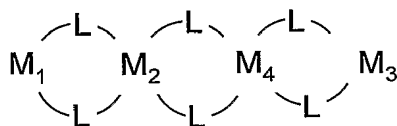
5   where M_4 is M_1 and L is a bridging ligand and in which the rare earth metals and the non rare earth metals can be joined together by a metal to metal bond and/or via an intermediate bridging atom, ligand or molecular group or in which there are more than three metals joined by metal to metal bonds and/or via intermediate ligands and

10   11. A device as claimed in any one of claims 3 to 10 in which $L\alpha$ has the formula (I) to (XVII) herein.

12. A device as claimed in any one of claims 3 to 11 in which Lp has the formula of figs. 1 to 8 of the accompanying drawings or of formula (XVIII) to (XXV) herein.

15

13. A device as claimed in claim 1 or 2 in which the organometallic chelate is a metal quinolate.

14. A device as claimed in claim 13 in which the metal quinolate is lithium quinolate,
20   aluminium quinolate, scandium quinolate zirconium quinolate, hafnium quinolate or vanadium quinolate.

15. A device as claimed in claim 14 in which the metal quinolate is doped with a fluorescent, phosphorescence or ion fluorescent compound.

25

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16. A device as claimed in claim 15 in which the dopant is diphenylquinacridine, diphenylquinacridone, coumarins, perylene or their derivatives.

17. A device as claimed in claim 1 or 2 in which the photovoltaic element has the formula
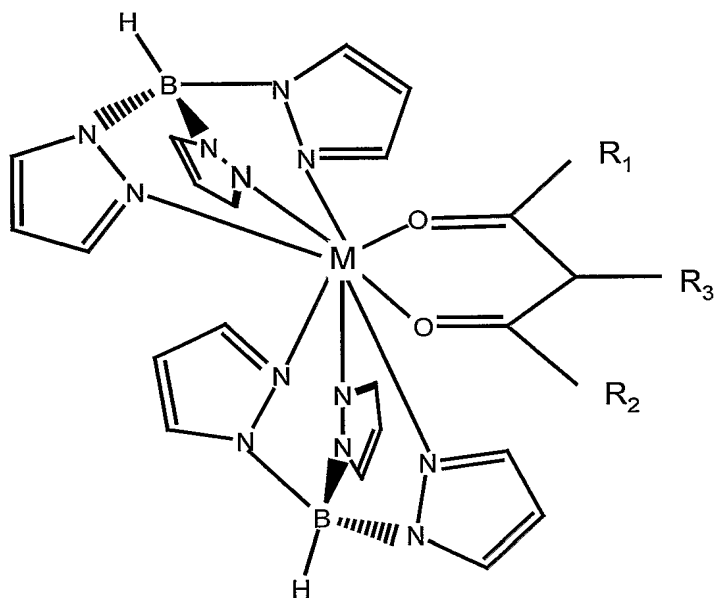
where M is a rare earth, transition metal, lanthanide or an actinide and R_1, R_2 and R_3 can be the same or different and are selected from hydrogen, and substituted and unsubstituted hydrocarbyl groups, substituted and unsubstituted aliphatic groups, substituted and unsubstituted aromatic, heterocyclic and polycyclic ring structures, fluorocarbons and trifluoryl methyl groups, halogens and thiophenyl groups.

18. A device as claimed in any one of claims 2 to 17 in which the second electrode comprises a transparent substrate which is a conductive glass or plastic material and which covers at least part of the pholtovoltaic element.

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19. A device as claimed in any one of the preceding claims which comprises sequentially (i) a first electrode comprising a metal, (ii) a plurality of layers of photovoltaic elements in which the photovoltaic elements in at least two of the layers are different and (iii) a second electrode.

5

20. A device as claimed in claim 19 in which at least some of the different photovoltaic elements absorb light at different wavelengths.
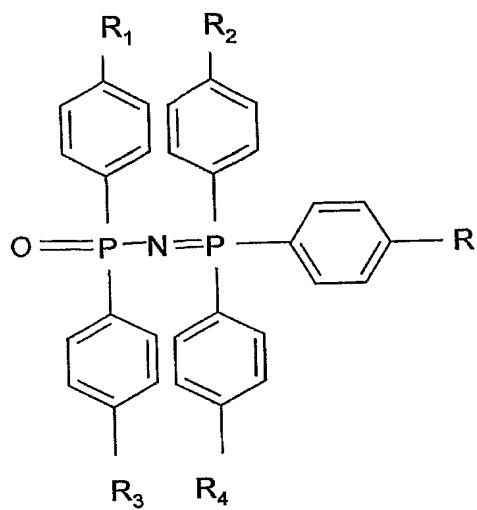
Fig. 1
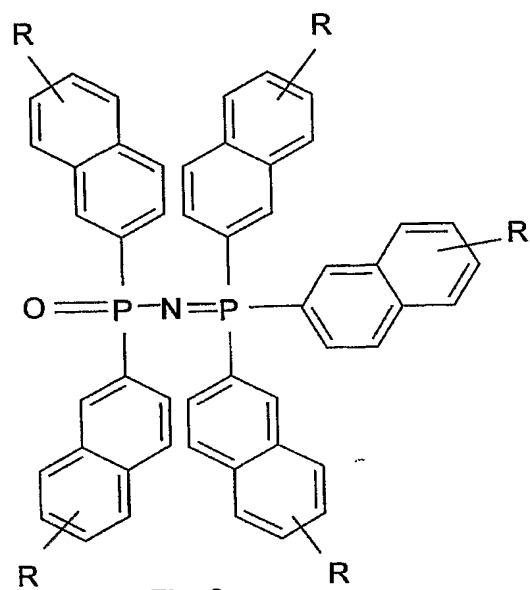
Fig. 2a
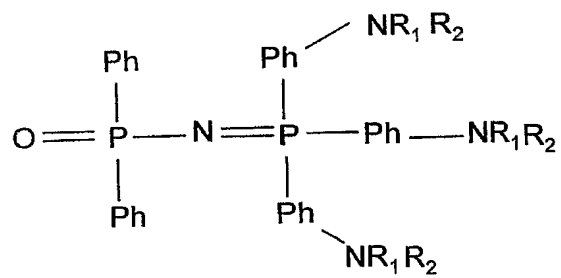
Fig. 2b
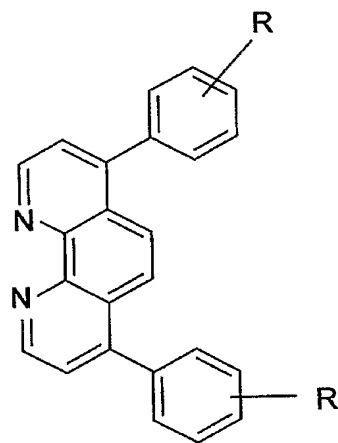
Fig. 3

2/24
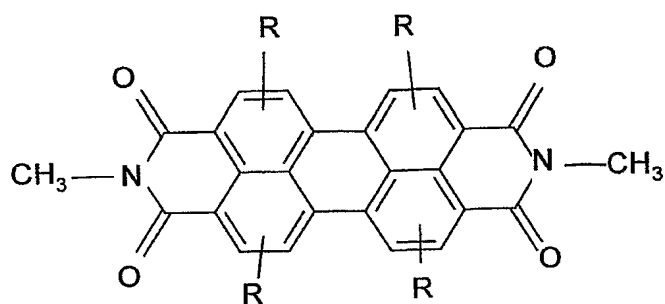
Fig. 4a
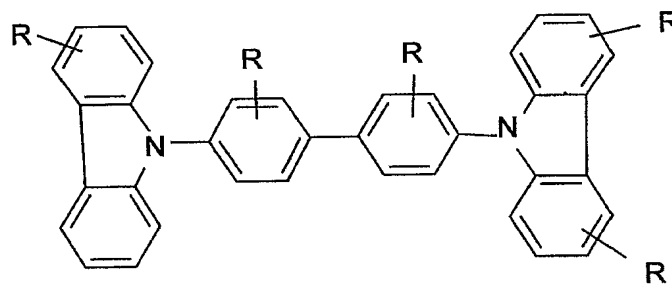
Fig. 4b
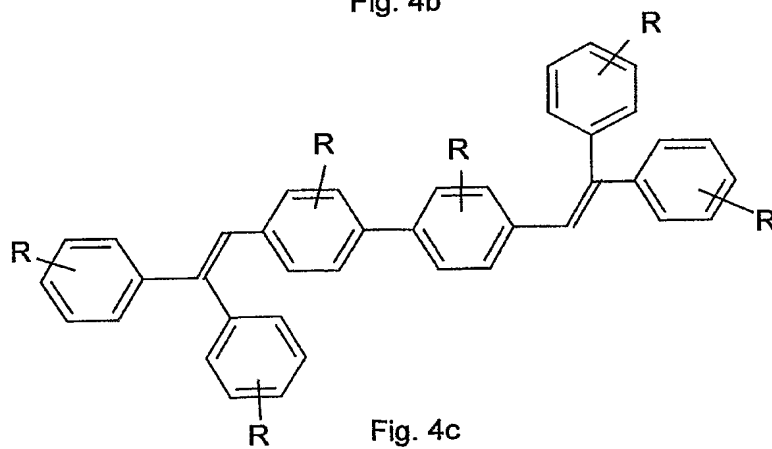
Fig. 4c

3/24
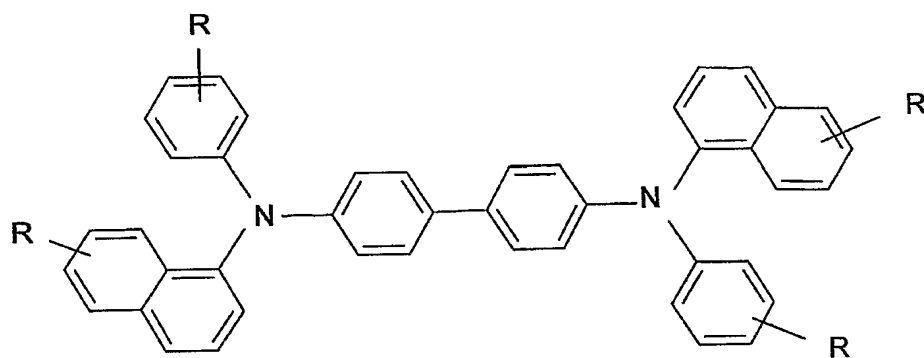
Fig. 4d
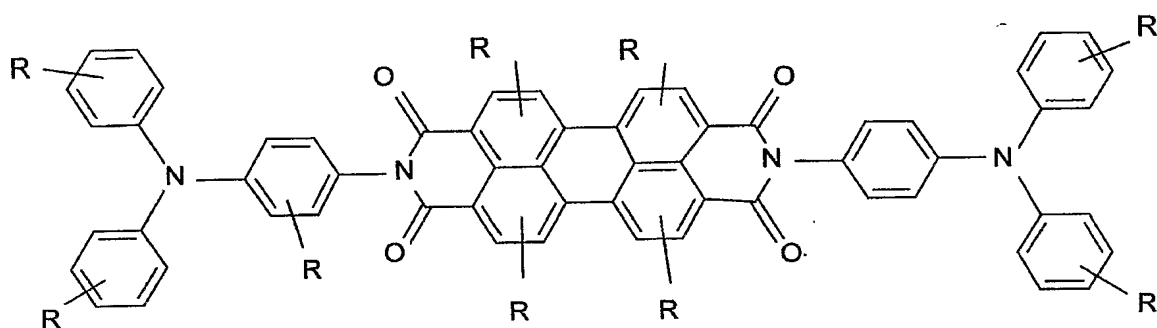
Fig. 4e
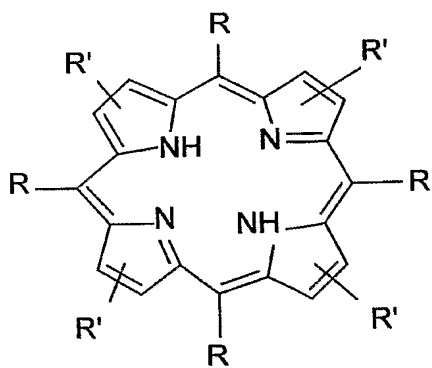
Fig. 4f
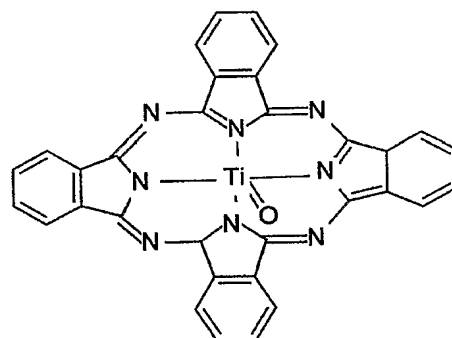
Fig. 4g
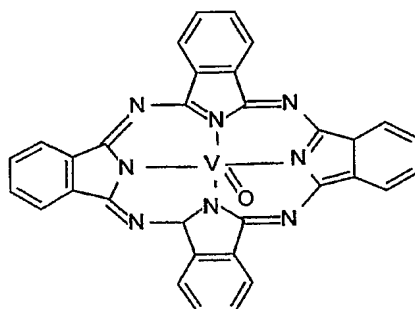
Fig. 4h
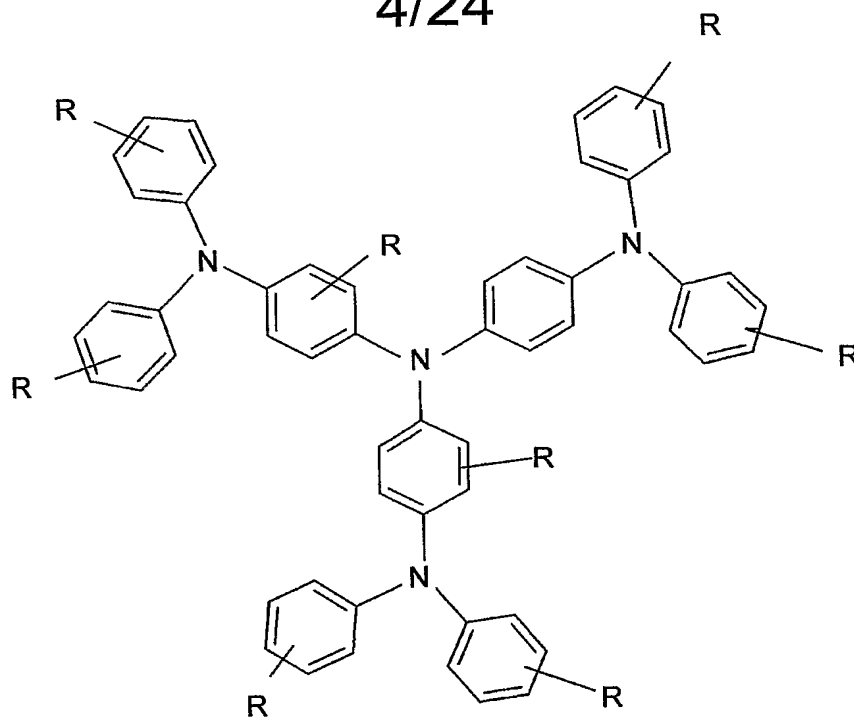
Fig. 4i
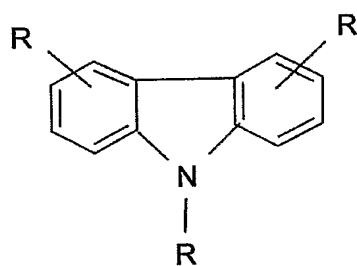
Fig. 4j
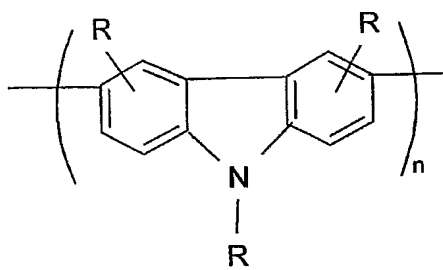
Fig.4k
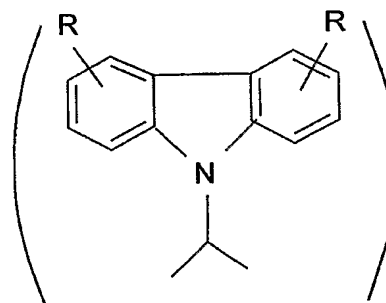
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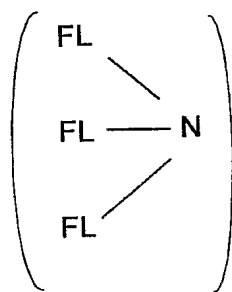
Fig. 5a
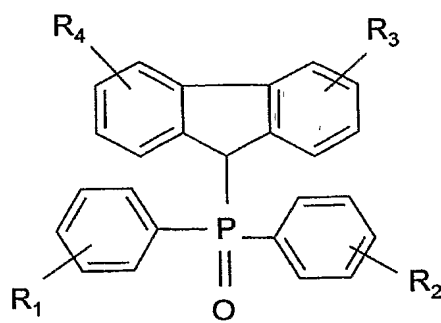
Fig.5b
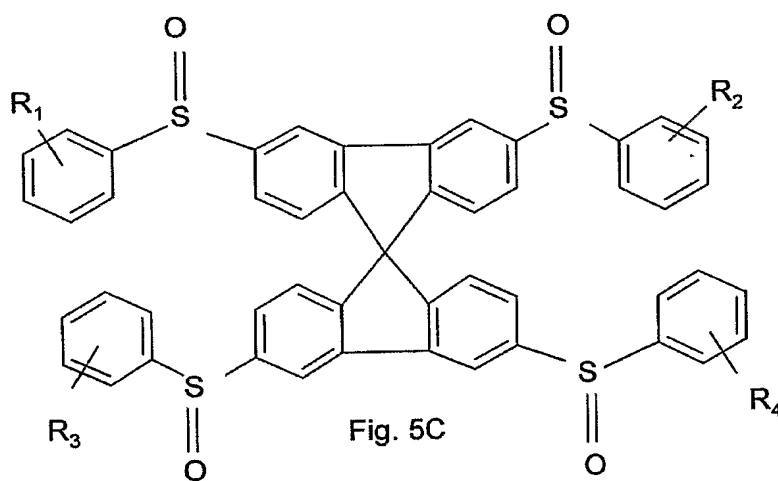
Fig. 5C
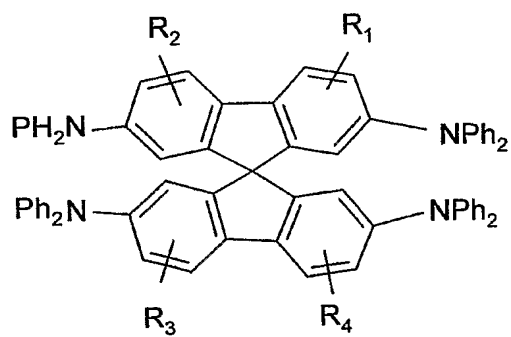
Fig. 5d

6/24
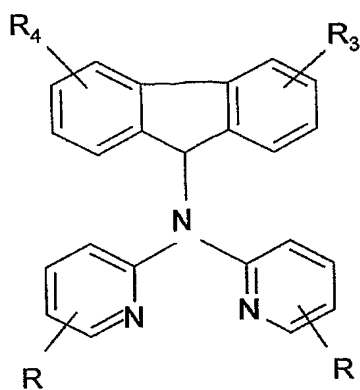
Fig. 5e
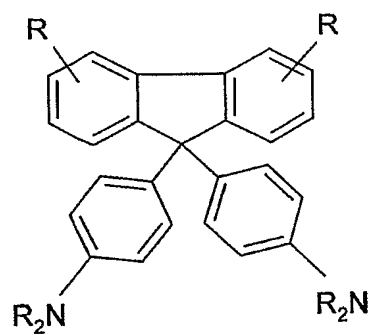
Fig 5f
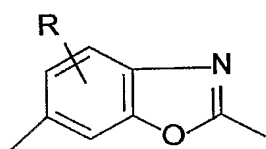
Fig. 6a
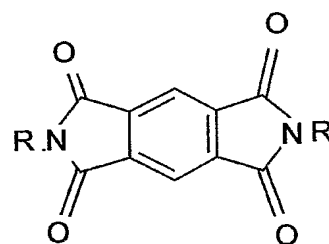
Fig 6b
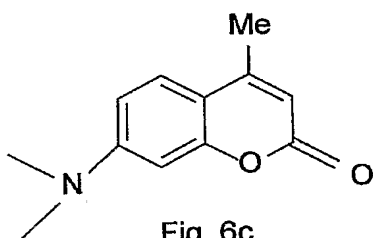
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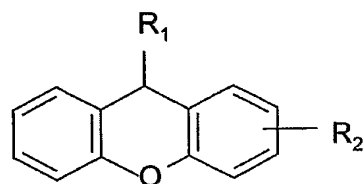
Fig. 6d
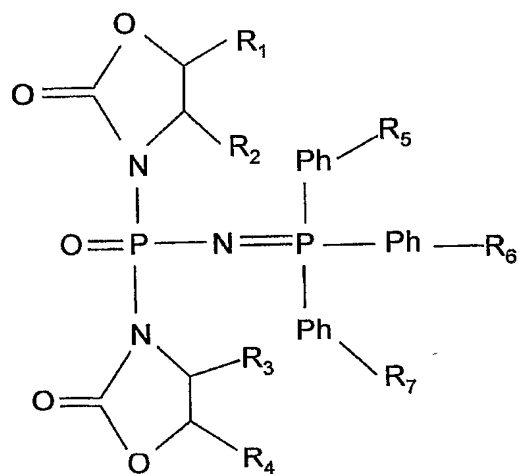
Fig. 6e
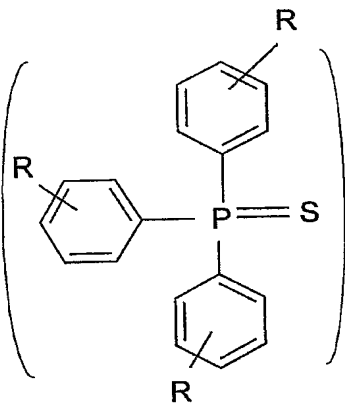
Fig. 7a

Fig. 7b

Fig. 7c

m= 0,1,2 etc.
n= 0,1,2 etc.

Fig. 7d

n = 0,1,2 etc.

Fig. 7e

m= 0,1,2 etc.
m= 0,1,2 etc.

Fig. 7f

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Fig. 8a

Fig. 8b

m= 0,1,2 etc.
n = 0,1,2 etc.

Fig. 8c

m= 0,1,2 etc.
n = 0,1,2 etc.

Fig.8d

Fig. 8e

m= 0,1,2 etc.
n = 0,1,2 etc.

Fig. 8f

m= 0,1,2 etc.
n = 0,1,2 etc.
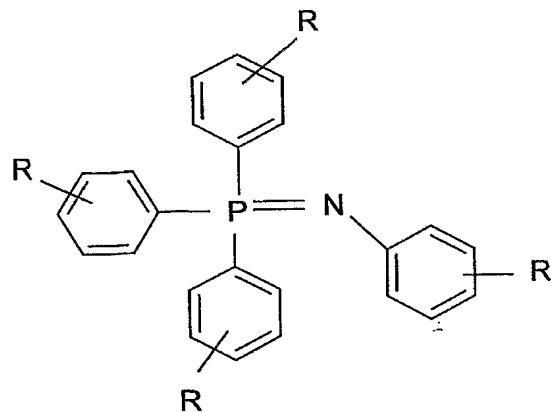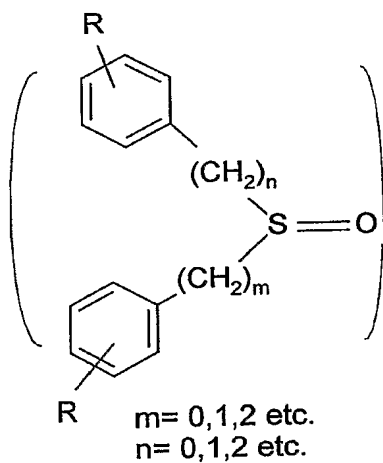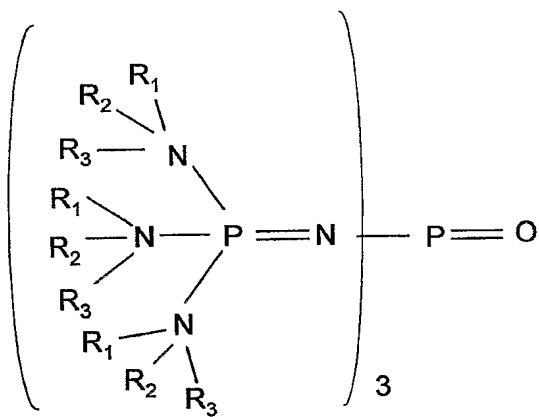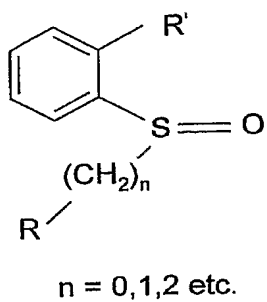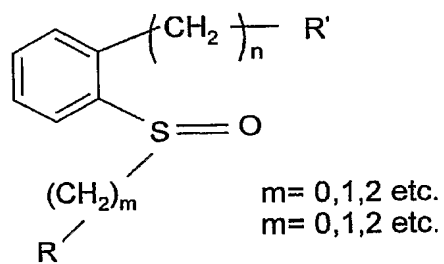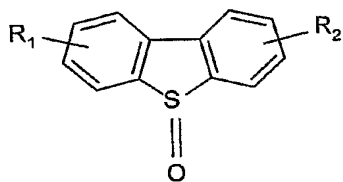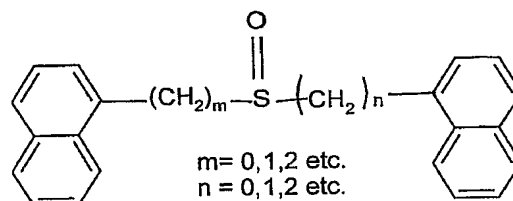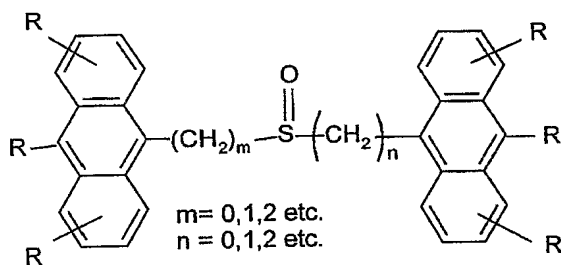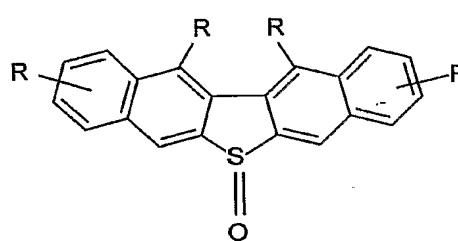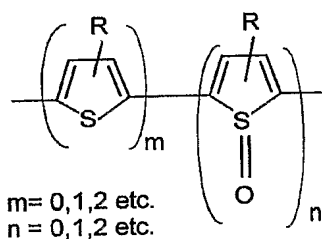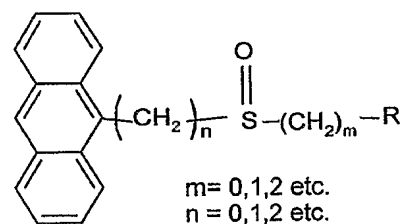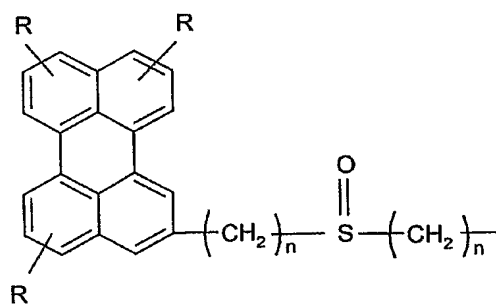
Fig. 8g
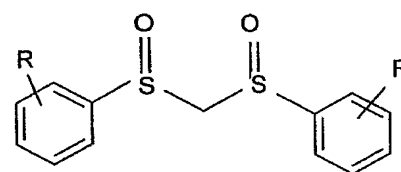
Fig. 8h

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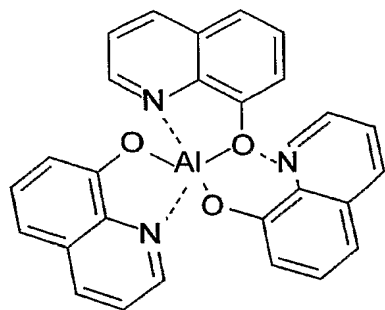
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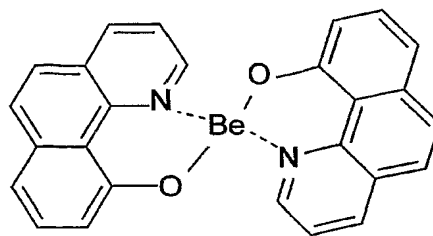
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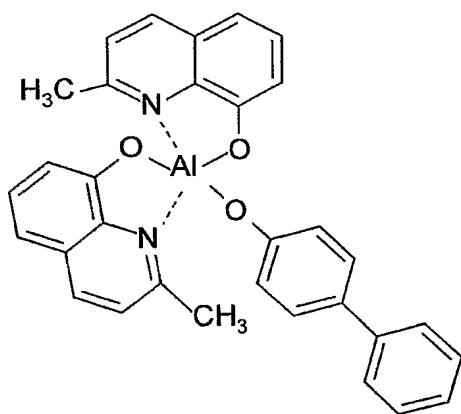
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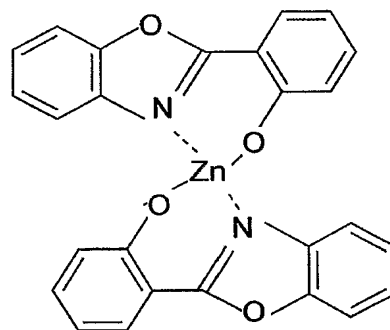
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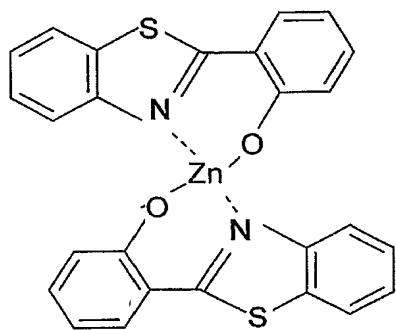
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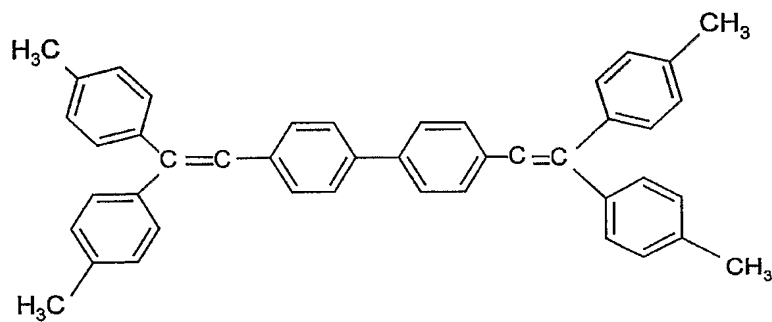
DTVb1

Fig. 9
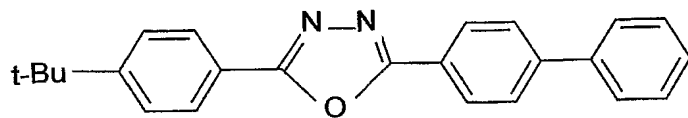
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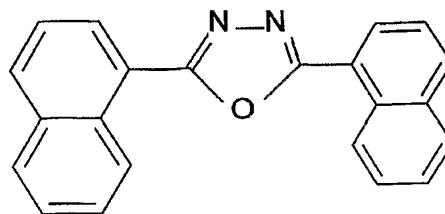
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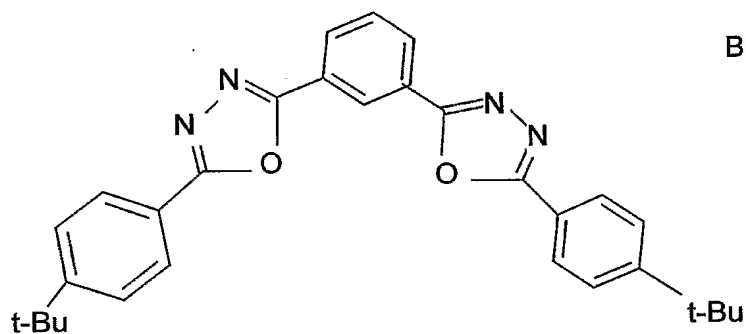
OXD-7

TAZ
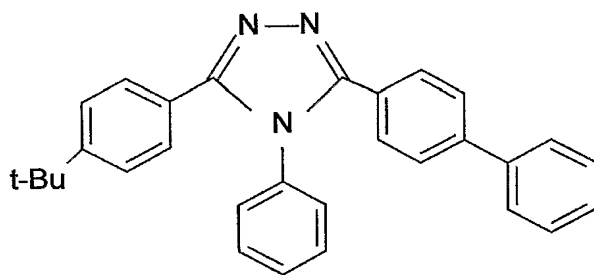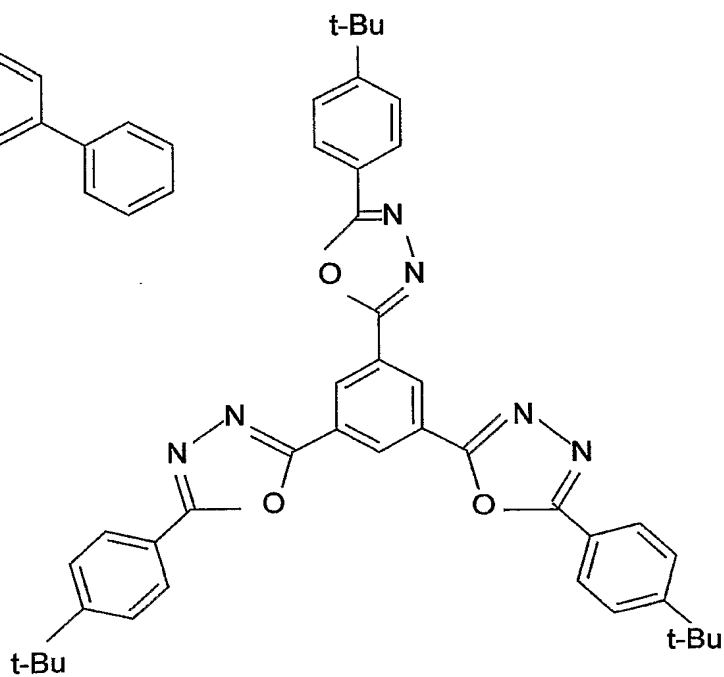
OXD- Star

Fig. 10

EDTA

DCTA

DTPA

TTHA

Fig. 11

Fig. 12a

Fig. 12b

Fig. 12c

Fig. 12d

Fig. 13a

Fig. 13b

Fig. 13c

Fig. 14a

Fig. 14b

or

Fig. 14c

Fig. 14d

Fig. 15a

Fig. 15b

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α -NPB

Fig. 16a

TPD

Fig. 16b

mTADATA

Fig. 16c

Fig. 17

Fig. 18

Fig. 19

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Fig. 20

Fig. 21

Fig. 22

Fig. 23

Fig. 24

(54) Title: DRUG DISCOVERY METHOD

(57) Abstract: A method of obtaining information about a chemically active area of a target molecule, for example for drug discovery, comprising: providing a set of substantially rigid chemical gauges; reacting said target with a plurality of gauges of said set of gauges; assaying a binding of said gauges with said target to obtain a plurality of assay results; and analyzing said assay results to obtain information about said chemically active area.

DRUG DISCOVERY METHOD

FIELD OF THE INVENTION

The present invention relates to methods of molecule affinity determination, for example, for use in discovering new drugs.

BACKGROUND OF THE INVENTION

The development of a new pharmaceutical, from conception to readiness for marketing, typically costs hundreds of millions of dollars and takes many years. The development process starts with a step of matching a molecule (a potential pharmaceutical) to a target, e.g., a protein in a human body or in a microorganism. The matching of a molecule to a pharmaceutical is known as a drug lead, as it may lead to the development of a drug. The molecule is then modified to be more active, more selective and more pharmaceutically acceptable (e.g., less toxic and more easily administered). The failure rates at these stages are very high.

With the development of combinatorial chemistry and automated screening techniques, a new method of drug discovery has been developed. In this new method, a large library of molecules is chemically tested against a target, with the molecule having a best match being used as a starting point for finding a lead and/or as a lead. Some of these libraries are constructed empirically, for example, based on available molecules and/or molecules known to act as pharmaceuticals. Other libraries are constructed to have a wide a range as possible of different molecules. Other libraries are constructed so that individual molecules will have as great a chance as possible in matching a target. In general, molecules are selected to be as diverse as possible and to be drug like (e.g., size, chemical behavior) so that if a match is found it can serve as a lead.

Some references to such libraries and/or other discovery methods include, Pickett S.D. at al., J. Chem. Inf. Comput. Sci. 36(6), p.1214-23 (1996) and Ferguson A.M. et al., J. Biomol. Scr. 1(2), p. 65 (1996), Bunin A.B. et. al., Proc. Natl. Acad. Sci. USA 91, p. 4708-12 (1994), Ellman J. et. al., Proc. Natl. Acad. Sci. USA 94, p. 2779-82 (1997) and Maly D.J. et. al., Proc. Natl. Acad. Sci. USA 97(6), p. 2419-24 (2000), the disclosures of which are incorporated herein by reference.

Another, virtual, structure based, type of screening is known. In the virtual method, a model of the target is generated (e.g., x-ray crystallography, estimated tertiary layout, analogy). Then, the affinity of a large number of molecules is determined by calculating docking behavior of a model of the molecule in the model of the target. Due to the relatively primitive

state of molecular modeling and the resulting lack of availability of models, this method is not currently very successful.

Sunesis, inc., in DJ Maly et al PNAS 97(6), p 2419-24(2000), the disclosure of which is incorporated herein by reference, suggest using large fragments of molecules as leads and then linking together such matching leads that are found into larger leads that are tested again for matching. The fragments are provided with pre-defined linkers, for the linking together.

PCT application PCT/US99/06734 (WO 99/49314), the disclosure of which is incorporated herein by reference, also describes a scheme of using fragments, and then linking the fragments to provide leads.

SUMMARY OF THE INVENTION

An aspect of some embodiments of the invention relates to a target characterization method, in which a plurality of small, measurement molecules interact with a target and the target is characterized based on an analysis of the interactions of the measurement molecules with the target. In an exemplary embodiment of the invention, none of the measurement molecules is used as a lead or as a fragment of a lead, nor are the molecules selected for interaction based on their drug-type diversity. Rather, the measurement molecules are selected based on their expected ability to measure various chemical and/or physical dimensions of the target. In an exemplary embodiment of the invention, while the number of measurement molecules is relatively small (e.g., $<10^6$), this number spans the space of characterization of the target molecule and can suffice to provide a relatively complete characterization of the target. In other embodiments, only a partial characterization is needed and/or obtained. Alternatively or additionally, while the measurement molecules are selected for span reasons, they are also used as leads or as fragments of a lead.

In an exemplary embodiment of the invention, a complete process of drug discovery comprises:

(a) selecting a target;

(b) optionally selecting a set of measurement molecules useful for the target, or using a universal library;

(c) characterizing the target using the set of measurement molecules;

(d) reconstructing a pharmaceutical model of the target, based on the characterization; and

(e) using the model to forward a discovery process, for example, select, reject, filter and/or design a drug lead.

In some embodiments of the invention, a typical measurement molecule can make one of several measurements, and a processing method, for example clustering, is optionally used to extract the particular measurements made by the molecules.

In an exemplary embodiment of the invention, the measurement molecules are a set of chemical gauges, of which some, typically a small number, bind to the target, typically at one or more active sites of the target. The binding of a gauge to the target can be determined using various assay methods, including substantially any of those known in the art, for example, by detecting a change in the chemical or biological behavior of the target or by detecting a reduction in the number of free gauge molecules in a sample. In a particular example, a functional assay for a protease (e.g., of an HIV protein) comprises linking a fluorescent molecule onto a protein (or other peptide). The protease is allowed to interact with a gauge, and this interaction is expected to reduce or counteract (or enhance) its affinity for the protein, which change in affinity may be determined by measuring the fluorescent properties (e.g., polarization) of the mixture of protein and protease. In an exemplary embodiment of the invention, each gauge is selected to have an affinity to one or more particular geometric layouts. In an exemplary embodiment of the invention, the total geometry of a target area is reconstructed from the determination of affinity (and/or lack of affinity) of a plurality of gauges.

In an exemplary embodiment of the invention, each of the gauges is constructed from a scaffold to which a plurality of particular chemical moieties are attached. Three such moieties define a triangle of moieties which includes both a definition of the moieties at the vertexes and the distance between the vertexes. In an exemplary embodiment of the invention, the scaffolds and moieties are selected so that the triangles are relatively rigid, however, some degree of play in the length of the triangle sides (inter-moiety distances) may be desirable.

Each such moiety triangle matches a particular spatial layout of three binding sites that match the moieties. Optionally, the distance between the moieties is varied for different gauges, so that a range of triangles with various desired combinations of moieties and distances between the moieties is provided. As will be shown below, a gauge library that includes a spanning set of such triangles, both with regards to distance and with regards to moiety is not prohibitively large.

In an exemplary embodiment of the invention, the scaffold and/or the moieties are selected to have a minimum flexibility, so that they more specifically define the geometric features that they match.

Optionally, the scaffolds and/or the moieties are selected to have a low molecular weight, so as to improve linking of low affinity gauges and/or targets and possibly provide information for such cases.

In an exemplary embodiment of the invention, when selecting gauges for a measurement library, some degree of overlap of moiety triangle is provided. For example, an repetition overlap factor of 2 or 3 maybe provided (e.g., each triangle appears in at least 2 or 3 gauges). This is expected to increase the probability of finding a triangle that binds, especially in view of problems which may occur such as steric clashes, chemical mismatch and/or solubility. Typically, an exact repetition of the moiety triangle is not available, so a nearly similar triangle is used for providing the overlap. In some cases, the triangles are selected so that for at least some pairs of moieties on the target, a triangle with a smaller distance between the same moieties and a triangle with a larger distance between the same moieties are both available for binding. This provides a non-repetition overlap factor. Alternatively to 2 or 3, a lower or higher overlap factor, for example 4 or 6, and/or possibly a fractional factor (e.g., an average overlap), may be used. The overlap may be uniform on the library, or a greater overlap may be provided for some triangles and/or molecules, for example for molecules where there is a greater probability of steric clashing due to the scaffold and/or other moieties, or based on experimental results which indicate that certain gauges and/or triangles are difficult to bind.

It should be noted that if a molecule is required to distort in order to bind, its likelihood of binding is typically lower. Thus, the actual overlap between two dissimilar triangles of two gauges may be non-uniform and dependent on the total binding probability. In general, if a probability of discovery of biding in an assay is negligible, it is assumed that the gauge does not bind. This helps define the range of distortion that can be used to define coverage and overlap. In some embodiments of the invention, the molecules are substantially rigid, so the cut-off of degree of distortion is more clearly defined and limited.

A particular exemplary drug discovery process in accordance with an exemplary embodiment of the invention, is as follows:

(a)   Synthesize a library of small molecules designed to span all possible 3-point pharmacophores (all combinations of 3 elementary chemical moieties and distances between them). This is a finite library which may include, for example ~100,000 compounds. This is termed a USL (Universal Screening Library), due to its generalized nature of ability (e.g., in some embodiments of the invention) to be used for mapping a wide range of targets for which small molecule drugs are designed.

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(b)   For any target, screen the USL against that target, looking for weakly active compounds (affinity of ~100 microM). Theoretical considerations and experimental data indicate that 100-1000 hits should be expected for any target.

(c)   Computationally analyze the active molecules, seeking:

1.   3-Point-Pharmacophores (3PP's) involved in binding of the hits.

2.   Reconstruction of the binding-site topography in terms of chemical moieties involved in binding. Generate the complete pharmacophore (~10-20 points) of the binding-site.

(d)   Computationally identify molecules that may compliment a large enough (e.g., 6-8 points for nanoMolar binding) subset of the full pharmacophore. Optionally, by knowing which parts of these molecules are not directly involved in binding, design them to meet predefined drug-like qualities (e.g. using Lipinski's rules of 5).

(e)   Using well known chemical knowledge, chose those molecules most amenable to synthesis and other considerations (e.g., toxicity) and synthesize those as possible drug candidates.

(f) Testing and iterations.

An aspect of some embodiments of the invention relates to estimating a spatial layout of binding locations in a target molecule. In an exemplary embodiment of the invention, the binding of a plurality of small molecules to the target is determined, for example using assay methods. In an exemplary embodiment of the invention, the small molecules are selected to have or are each modeled as a set of geometrical sub-structures which may, on its own, bind to the target. In one example, the geometrical sub-structure may be three moieties arranged in a triangle. In an exemplary embodiment of the invention, the assay results are analyzed to determine which of the many geometrical sub-structures in the small molecules, actually bind to the target molecule. In an exemplary embodiment of the invention, a clustering method is used to determine which geometrical sub-structures bind, by clustering together molecules that bind and that have similar geometrical sub-structures. The output of the clustering method may be a list of all the probably binding sub-structures. Optionally, the sub-structures used for analysis and for design of the gauges is triangular.

In an exemplary embodiment of the invention, a score based method is used to convert a list of geometric sub-structures (e.g., triangles) into a complete geometric structure, by:

(a) generating possible structures from the list of sub-structures;

(b) associating a "correctness" score with each structure; and

(c) selecting between structures based on their score.

In an exemplary embodiment of the invention, the score represents the probability of two sub-structures sharing a portion in the structure and, optionally, a higher score is provided for a structure in which a portion is shared, as that represents a more cohesive structure. Alternatively or additionally, the score represents the probability of two different moieties binding to a same binding location, and, optionally, a higher score provided if more moieties share a same binding site, as this represents a minimization of pharmacophore points to the minimum required. Other heuristic rules may be used as well.

In an exemplary embodiment of the invention, the set of all potential models is not actually built. Instead a search is made of the space of models and the models are built (and/or rejected) ad-hoc based on the determined sub-structures.

In an alternative embodiment of the invention, a clustering method is used, comprising for example:

(a) generating (all) possible structures from the found triangles, optionally using particular construction rules;

(b) finding the most common large sub-structures that are shared by multiple structures; and

(c) selecting a particular common sub-structure, optionally using a scoring method, such as cluster size, edge size and thresholding of cluster size, possibly selecting a most common substructure from all those that pass a certain threshold. In some cases, more than one final resulting sub-structure will be provided.

It should be noted that an actual pharmacophore may not be a limited size and strictly defined entity, for example, a point that is technically outside the active area, can act as a pharmacophore if a small molecule drug binding to that point includes a tail that blocks the active area from interacting with the substrate. Often however, the "relevance" of a binding area will decrease as the area is further away from an active area, a control area and/or a conformance changing area. In addition, the binding affinity of a protein is often significantly smaller away from such areas.

In an exemplary embodiment of the invention, the structures for clustering are generated in the following manner:

(a) a triangle is selected as a base sub-structure;

(b) a point is added to the base sub-structure, if there are two triangles that, together with a triangle on the sub-structure, define a tetrahedral; and

(c) (b) is repeated until there are no unused triangles left to add.

An aspect of some embodiments of the invention relates to finding one or more molecules (e.g., a drug lead) that is expected to match a target, from a plurality of geometric and/or chemical measurements of the target area. The measurements are optionally used to generate a reconstruction model of the target, against which model various processing methods may be applied, for example using suitable computer hardware or software. In an exemplary embodiment of the invention, the measurements are provided by interacting the target with a plurality of gauge molecules and determining the degree of binding of the gauge molecules to the target. For example, a set of triangular geometries is determined by gauge matches and is correlated to recreate a three-dimensional model of the target area.

Optionally, the target area is compared to structures of known pharmaceuticals or pharmaceutical like materials, for example a drug lead library. Alternatively or additionally, the target area geometry is used to select a most likely candidate from a relatively small plurality of materials. Alternatively or additionally, the matching is used during the process of drug development, to select or reject modifications of drug leads, which do or do not match the target area geometry.

In a particular example, if one wants to satisfy Lipinski's rules by adding or subtracting H-bond donors/acceptors, knowing which ones are important for binding would indicate which ones not to remove, and knowing which parts of the molecule are not important would indicate where additions can be made without hurting the binding.

An aspect of some embodiments of the invention relates to a library of gauges for measuring a biochemical target. In an exemplary embodiment of the invention, the library comprises a large number of molecules constructed by attaching moieties on a relatively small number of scaffolds. In an exemplary embodiment of the invention, the moieties are selected to have as low a molecular weight as possible. Alternatively or additionally, the library is designed to cover, in a desired manner, a set of parametrically defined geometric sub-structures. Possibly, the geometric sub-structures are triangles, with different moieties at their vertexes. In one example, the range of different triangle dimensions is evenly covered.

In an exemplary embodiment of the invention, the library is selected to provide same (overlapping) geometric sub-structures based on several scaffolds and/or in several molecules, for example, each sub-structure being provided twice or thrice. Optionally, the overlapping is designed to take into account steric clashes and/or different chemistries of different scaffolds and/or gauges.

In an exemplary embodiment of the invention, the scaffolds used include at least two, at least five, at least seven, at least 10 or any greater or intermediate number, such as at least all of the following scaffolds: mono-carbone; pyrrole; quinoline pyrazinoquinazoline; isoindoloindole; isoindoloindole with an oxygen moiety attached; indolo[2,3-b]quinoline; pyrrolizine; 2,2'-bipyrrolone; indolizine; Thiophene; 1H-Pyrrole; Furan; Benzene; Pyridine; Pyrimidine; Pyrazine; 6H-Thieno[2,3-b]pyrrole; 1,6-Dihydro-pyrrolo[2,3-b]pyrrole; 1H-Indole; Thieno[2,3-d]pyrimidine; 6,7-Dihydro-pyrazolo[1,5-a]pyrimidine; Quinoline; Isoquinoline; Quinoxaline; 3,4-Dihydro-benzo[e][1,4]diazepin-5-one; 3,8-Dihydro-4H-pyrrolo[2,3-e][1,4]diazepin-5-one; 3,4-Dihydro-thieno[2,3-e][1,4]diazepin-5-one; 3,6-Dihydro-4H-pyrrolo[3,2-e][1,4]diazepin-5-one; 5H,11H-Dibenzo[b,f][1,5]diazocine-6,12-dione; 1,4-Dihydro-10H-1,4,10-1,4,10-triaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione; 4H,10H-1-Thia-4,10-diaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione; Dipyrrolo[1,2-c;2',1'-e]imidazol-5-one; 1,4,7,9-Tetrahydro-1,4,6,9-tetraaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 4,7,9-Trihydro-1-thia-4,6,9-triaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 2,4,9,Trihydro-11lambda*4*,6-dithia-4,9-diaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 6,9-Dihydro-5H-1-thia-5,8,9,triaza-cyclopenta[a]azulen-4-one; 3,10,Dihydro-4H-[1,4]diazepino[5,6-b]indol-5-one; 3,6-Dihydro-4H-[1,4]diazepino[6,5-b]indol-5-one; 7,8-Dihydro-1H-1,7,10-triaza-cyclohepta[e]inden-6-one; 8,9-Dihydro-3H-3,6,9-triaza-cyclohepta[e]inden-10-one; 7,8-Dihydro-1H-1,5,8-triaza-cyclohepta[f]inden-9-one; 8,9-Dihydro-5,6,9,11-tetraaza-cyclohept[b]naphthalene-10-one; 3,4-Dihydro-[1,4]diazepino[5,6-b]quinolin-5-one; 8,9-Dihydro-4,8,11-triaza-cyclohepta[a]naphthalene-7-one; 11H-10,11-Diaza-benzo[b]fluorine; α-hydroxyacids; α-aminoacids; cohels; Bicyclo[2.2.2]octane; 2-Methylene-2,3-dihydrobenzo[1,4]dioxine; 6,7-Dihydro-2H-pyrazino[1,2-a]pyramidine; 9H-Fluorene; 1,4-Diaza-bictclo[2.2.2]octane; 1-Aza-bicyclo[2.2.2]octane; Pyrido[2,3-d]pyrimidine; 5-Methylene-1,5-dihydro-pyrrol-2-one; Bezno[4,5]imidazo[1,2-a]pyrimidine; 1,4-Dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine; 4,10-Dihydro-1,4a,10-triaza-phenanthren-9-one; 1,5-Dihydro-imidazo[1,2-a]pyrimidin-2-one; 1,2,3,5-Tetrahydro-imidazo[1,2-a]pyrimidine; Thiazolo[3,2-a]thieno[2,3-d]pyrimidin-5-one; 1,9-Dithia-4a,10-diaza-cyclopenta[b]fluoren-4-one; 5,6-Dihydro-1-thia-5,7,8,9a-tetraaza-cyclopenta[e]azulen-4-one; 6,10-Dihydro-5H-1-thia-5,7,10a-triaza-benzo[e]azulen-4-one; 4,5-Dihydro-3-thia-4,5a,10-triaza-cyclopenta[a]fluorine; 8H-1-Thia-cyclopenta[a]indene; 3-Thia-4,5a,10-triaza-cyclopenta[a]fluorine; 6,7,9,11-Tetrahydro-10-thia-6,9-diaza-indeno[1,2-a]azulene-5,8-dione; 2,3,6,7,12a-Hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione; 5,10-Dihydro-4H-

2,3a,10-triaza-cyclopenta[a]fluorine; 5H-Pyrido[4,3-b]indole; 11H-Indolizino[1,2-b]quinolin-9-one;   1,2-Dihydro-2,4a,9,-triaza-anthracene-3,10-dione;   6H-Isoindolo[2,1-a]indole;   1,5-Dihydro-benzo[b][1,4]diazepin-2-one; 5,10-Dihydro-dibenzo[b,e][1,4]diazepin-11-one; 5,11-Dihydro-benzo[e]pyrido[3,2-b][1,4]diazepin-6-one;   4,9-Dihydro-3-thia-4,9-diaza-benzo[f]azulen-10-one;   Benzo[g]quinoxaline;   Pyrazino[2,3-b]quinoxaline;   Pyrido[2,1-b]quinazolin-11-one; 1-Thia-4a,9-diaza-cyclopenta[b]naphthalene-4-one; 2-Methylene-4H-benzo[1,4]thiazin-3-one.

In general, the greater the number of scaffolds, the easier it is to find right sizes of gauges and also deal with a wider range of steric clash conditions and/or different chemistries. On the other hand, smaller number of scaffolds, promotes uniformity of chemical behavior and synthesis methods.

In an exemplary embodiment of the invention, the moieties used include, at least 2, at least 4, at least 6, or any greater number, such as all of the following moieties: Me, Et, Pr, Ph, CO_2H, OH, NH_2, ketone, halides, such as Cl or Br, other acids such as SO_3H, PO_3H_2, and NH-C=NH(-NH_2) (Guanidine).

In general, using more moieties may provide greater accuracy in characterizing binding, at a possible expense of library size. Using fewer moieties may also simplify synthesis methods.

An aspect of some embodiments of the invention relates to selecting a gauge library for use in characterizing a target. In an exemplary embodiment of the invention, a range of dimensions of target geometries is estimated, as well as bond types of binding locations. A set of molecules that spans the range of possible sizes and bond types is selected from a larger available set of molecules. The selection may be, for example, electronic with selected molecules being synthesized in response to selection or the selection is physical, with the gauge molecules already available. Optionally, the estimation uses various information known about the target. Alternatively or additionally, the estimation is made using a first screening library, that is, for example, more flexible in the affinity of its bond types and/or uses molecules that are more flexible.

Optionally, the gauges are selected so that the library will have considerable repetition, for example to overcome steric clashes and/or other properties of the molecules, that might prevent binding. Optionally, the library includes at least one, or possibly more than one multi-point binding geometries, for at least some of the physical geometries, for example, triangles and pentagons.

In accordance with exemplary embodiments of the invention, such a library can be used on its own or as part of a different library for various uses. In an exemplary embodiment of the invention, such a spanning library is used to increase the probability of binding of any of the gauges in the library to the target, desirably, a considerable number of gauges. It is noted that a standard lead library often provides no bindings at all. Optionally, the bindings results are used to gather information about the target, especially statistical information. Optionally, the statistical information is used to provide structural information about the target. Optionally, the structural information comprises a chemical and/or geometrical structure of a significant part of the target, for example, an active area thereof. It should be noted that in an exemplary embodiment of the invention, once even a single binding is found, useful information about the target is available and any library that assists in guaranteeing this binding has a use.

An aspect of some embodiments of the invention relates to designing and/or creating a gauge library for use in characterizing target molecules by geometrical and/or chemical measurements.

In an exemplary embodiment of the invention, library construction comprises:

(a) identifying molecules that may be suitable as gauges;

(b) determining if the identified molecules provide required gauges; and

(c) verifying that the molecules are realistic, for example being readily synthesizable and/or having desirable chemical behavior. It should be noted that this order is flexible, for example as shown below.

In one example, this method is used when basing at least part of a gauge library on existing libraries. In some libraries, (c) is already performed when the library is originally composed. Further, in some case, rather than select molecules, known existing binding results of certain molecules are used as input, instead of selecting a gauge and physically testing the binding affinity.

Alternatively, candidate gauges may be provided as a group, for example, when a new scaffold is added to a library. A large number of candidates then arise, as attachments of different moieties to the scaffold. In this case, however, an opposite step may be taken - a scaffold may be rejected because it does not add any (or enough) gauges that do not overlap with existing gauges. For some parts of the spanned space, scaffolds that generate few gauges may be suitable.

In an alternative method, chemical design methodology is applied to design gauges and/or scaffolds that have desired properties and/or geometries, for example, to fill in missing parts of a measurement space.

In an exemplary embodiment of the invention, one or more of the following are considered to be desirable properties of gauges, however, a gauge need not have all or even any of the following properties, in order to be useful for some embodiments of the invention:

(a) High rigidity. This may allow measurements to be more exact, however, a small degree of flexibility may be desirable, to allow complete coverage of all the space. Rigid means that the length and/or relative angles of the bonds do not change a significant amount.

(b) Low mass. This may increase the chance of bonding even if affinity is low and only three points on the gauge bind.

(c) Small size. This may allow targets to be more easily measured and steric clashes more easily avoided.

(d) Non-toxic. This may allow the use of the gauge in living cells. However, due to the differing sensitivity of different cells, this often cannot be ensured.

(e) Good chemical behavior. This means that the gauge is soluble and binds under conditions that do not distort the gauge, or distort it by a known amount.

(f) Strong binding. This means in one embodiment of the invention, for example, 1-100 micromolar, which is useful for example if solubility is low or toxicity is high.

In an exemplary embodiment of the invention, one or more of the following are considered to be good properties of scaffolds, however, a scaffold need not have all or even any of the following properties, in order to be useful for some embodiments of the invention:

(a) Easy to attach moieties (e.g., synthesize gauges) and obtain pure solutions of particular gauges.

(b) Provide a wide range of sizes.

(c) Have many (e.g., ≥3, better >4, >5) attachment points. While every hydrogen atom in a molecule is potentially an attachment point, in an exemplary embodiment of the invention, a useful attachment point is accessible for chemical manipulation.

(d) What (relatively rare in other gauges) chemistries possibilities and/or gauge sizes are added to the library, by inclusion of the scaffold.

(e) Allow attachment of various combinations of moieties, as not all combinations will work with all scaffolds.

In an exemplary embodiment of the invention, one or more of the following are considered to be desirable properties of a gauge library:

(a) Spanning of a range of distances between bonds.

(b) Chemical spanning. At points on opposite ends of bonds, a wide range of moieties are provided.

(c) Sub-structure spanning. For the sub-structure selected, e.g., a triangle, all possible triangle configurations in a target can bind to at least one gauge in the library.

(d) Small. The smaller the library the better. For practical reasons, the library cannot be too small, however, very large libraries are generally not necessary.

(e) Variations of gauge properties within library to match the density of gauge coverage, for example, less rigid bond lengths to cover missing or spaced apart bonds.

(f) Uniform coverage. Various types of uniformity may be provided, for example, uniformity in absolute sizes or uniformity corrected for chemical dependencies. For example, the density of distances for short bond lengths will be higher than for long bond lengths, to provide a same normalized density for different lengths.

(g) Degree and type of overlap. While more overlap is generally better for reconstruction and chemical generalization, it often comes at a cost of library size and cost. An overlap of three (e.g., each triangle is provided in three gauges) is an exemplary compromise.

In general, however, the desirable properties may depend on the target, environment and/or type of discovery method being applied. In particular, it is noted that in some cases, the generated library is only partial, for example spanning only a part of the space, being suitable for only part of a target, being in a lower resolution, having less (or no) overlap and/or being prone to fail for some types of targets.

A broad aspect of some embodiments of the invention relates to molecules, such as gauges and scaffolds and methods of synthesis thereof, which may find use for libraries in accordance with exemplary embodiments of the invention.

There is thus provided in accordance with an exemplary embodiment of the invention, a method of obtaining information about a chemically active area of a target molecule, comprising:

providing a set of substantially rigid chemical gauges;

reacting said target with a plurality of gauges of said set of gauges;

assaying a binding of said gauges with said target to obtain a plurality of assay results; and

analyzing said assay results to obtain information about said chemically active area. Optionally, said gauges allow rotation of moieties of said gauges. Alternatively or additionally, said gauges are constructed using a rigid scaffold.

In an exemplary embodiment of the invention, constituent atoms of said gauges do not

5   move more than 1 Å unless at least 20Kcal/Mol are applied to the gauge.

In an exemplary embodiment of the invention, analyzing comprises identifying a plurality of spatial and chemically specific bindings configurations in said target active area. Optionally, said configurations comprise triangular configurations. Alternatively or additionally, identifying comprises identifying a configuration that matches a configuration of

10   a bound gauge. Alternatively or additionally, identifying comprises identifying a configuration that does not match a configuration of a bound gauge. Optionally, identifying comprises identifying by statistical analysis of said assay results. Optionally, identifying comprises identifying by clustering.

In an exemplary embodiment of the invention, identifying comprises assuming each

15   gauge indicates a single configuration. Alternatively or additionally, identifying comprises assuming at least some of the gauges indicate a plurality of configurations. Alternatively or additionally, identifying comprises classifying gauges by chemical moieties at vertexes of said configurations.

In an exemplary embodiment of the invention, the method comprises reconstructing a

20   spatial map of at least part of said chemically active area, from at least two of said assay results, said part including at least four chemical binding areas. Optionally, said part includes at least six chemical binding areas.

In an exemplary embodiment of the invention, the method comprises reconstructing a spatial map of at least part of said chemically active area, from at least two of configurations,

25   said part including at least four chemical binding points. Optionally, said part includes at least six chemical binding areas.

In an exemplary embodiment of the invention, reconstructing comprises:

test-reconstructing a plurality of spatial maps from said configurations;

scoring said maps; and

30   selected a spatial map based on its score. Alternatively or additionally, reconstructing comprises:

test-reconstructing a plurality of spatial maps from said configurations;

clustering said maps according to common substructures; and

selected a spatial map based on a relative property of a cluster it belongs to. Optionally, said relative property comprises size.

In an exemplary embodiment of the invention, said spatial map includes enough binding points to ensure binding of a small molecule drug having a chemical profile matching the binding points. Optionally, said spatial map includes at least 6 binding points. Optionally, said spatial map includes at least 8 binding points.

In an exemplary embodiment of the invention, said set of gauges comprises a set of gauges with at least 10,000 gauges. Optionally, said set of gauges comprises a set of gauges with at least 50,000 gauges.

In an exemplary embodiment of the invention, said gauges comprise moieties arranged in spatial configurations and wherein said gauges are selected to span a virtual space of spatial chemical configurations.

In an exemplary embodiment of the invention, substantially each point of virtual space that is spanned by said gauges is covered by at least two gauges. Optionally, substantially each point of virtual space that is spanned by said gauges is covered by at least three gauges.

In an exemplary embodiment of the invention, at least 0.5% of said gauges bind with said target. Optionally, at least 1% of said gauges bind with said target. Optionally, at least 3% of said gauges bind with said target.

In an exemplary embodiment of the invention, at least 50% of said gauges are defined by adding moieties to a set of fewer than 100 scaffolds. Optionally, at least 50% of said gauges are defined by adding moieties to a set of fewer than 50 scaffolds.

In an exemplary embodiment of the invention, at least said set of gauges uses fewer than 15 different chemical moieties to define the chemical behavior of said gauges.

In an exemplary embodiment of the invention, , at least said set of gauges uses fewer than 10 different chemical moieties to define the chemical behavior of said gauges.

In an exemplary embodiment of the invention, said assay is a functional assay. Alternatively or additionally, said assay is a binding assay. Alternatively or additionally, said assay is a cellular assay. Alternatively or additionally, said assay is a flow-through assay.

In an exemplary embodiment of the invention, said functional assay is performed in the presence of a natural substrate of said target..

In an exemplary embodiment of the invention, said target comprises a protein including a biochemically active area adapted to engage a substrate. Optionally, said chemically active

area comprises an area including said biochemically active area. Alternatively or additionally, said chemically active area comprises a control area of said protein.

In an exemplary embodiment of the invention, analyzing comprises analyzing successful binding of at least 60 gauges. Alternatively or additionally, analyzing comprises analyzing successful binding of at least 10 gauges. Alternatively or additionally, analyzing comprises analyzing successful binding of at least 100 gauges.

In an exemplary embodiment of the invention, identifying comprises identifying at least 40 different configurations. Alternatively or additionally, identifying comprises identifying at least 10 different configurations. Alternatively or additionally, identifying comprises identifying at least 100 different configurations.

In an exemplary embodiment of the invention, the method comprises:

comparing said map to a lead data base; and

selecting a lead from said data base for further use responsive to a semblance or lack of semblance between said lead and said map.

Alternatively or additionally, the method comprises:

comparing said map to a lead data base; and

rejecting a lead from said data base for further use responsive to a semblance between said lead and said map.

Alternatively or additionally, the method comprises:

constructing a lead to have a semblance to said map. Optionally, constructing comprises constructing using said gauges or scaffolds used to define said gauges.

In an exemplary embodiment of the invention, the method comprises:

comparing said configurations to a lead data base; and

selecting a lead from said data base for further use responsive to a matching of said configurations to said lead.

In an exemplary embodiment of the invention, the method comprises constructing a lead based on said configurations.

In an exemplary embodiment of the invention, the method comprises selecting at least one of said gauges as a lead for drug discovery.

In an exemplary embodiment of the invention, the method comprises comparing the binding of gauges with similar binding geometries to obtain steric clashing data; and

analyzing said steric clashing data to provide geometrical information about said target.

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There is also provided in accordance with an exemplary embodiment of the invention, a method of identifying the existence of a plurality of chemical-spatial configurations in a target, comprising:

5   assaying the target with a plurality of gauges having know chemical-spatial configurations at vertexes thereof, to provide a plurality of assay results;

defining an array of spaces, one space for each set of chemical behaviors of the vertexes of each configuration;

indicating said results according to said spaces, to generate clusters; and

identifying the existence of a configuration in said target from said clusters. Optionally,
10   indicating comprises spreading an indication responsive to a spreading function. Optionally, said spreading function is dependent on an estimated energy of binding of a gauge to said target.

There is also provided in accordance with an exemplary embodiment of the invention, a method of reconstructing a spatial shape of a chemical binding configuration of a target from
15   a set of sub-shapes, each of which indicates a part of said binding configuration, comprising:

selecting a base from said sub-shapes;

selecting at least two sub-shapes having the property that they match each other at least along one side thereof and match said base along another side thereof;

accumulating said sub-shapes to said base; and

20   repeating said selecting and said accumulating until all of said sub-shapes are used or cannot be used, thereby providing a shape of a binding configuration of said target. Optionally, the method comprises variationally repeating said selecting, accumulating and repeating using a different order of selection of sub-shapes. Optionally, the method comprises repeating said selecting a base and said variationally repeating for a plurality of different base selections.
25   Optionally, the method comprises clustering a plurality of such shapes according to shared sub-component shapes. Optionally, the method comprises selecting a sub-component shape as a resulting shape based on said clustering.

In an exemplary embodiment of the invention, said sub-shapes comprise triangles. Alternatively or additionally, said sub-shapes define chemical behavior at their vertexes and
30   wherein two sides are said to match if the chemical behavior at their vertexes match.

In an exemplary embodiment of the invention, two sides are said to match if their length is similar.

There is also provided in accordance with an exemplary embodiment of the invention, a method of selecting a scaffold for use in generating a part of a screening library, comprising:

providing a potential scaffold molecule including a plurality of possible attachment points for moieties;

5   determining a rigidity of the molecule; and

rejecting said potential scaffold molecule responsive to a lack of rigidity of said scaffold. Optionally, said lack of rigidity is absolute. Alternatively, said lack of rigidity is relative to other potential scaffolds.

In an exemplary embodiment of the invention, the method comprises selecting a

10   scaffold based on a number of rings thereof.

In an exemplary embodiment of the invention, the method comprises:

determining a plurality of gauge molecules that can be generated by adding moieties to said potential scaffold molecule;

determining for an existing library portion what spatial chemical configurations are

15   added by said molecules; and

selecting said potential scaffold molecule if one or more significant spatial chemical configurations can be added by it to said library portion. Optionally, the method comprises selecting a scaffold based on a number of configurations added by said scaffold. Alternatively or additionally, said significant spatial configurations are configurations not previously

20   provided or overlapped with,

There is also provided in accordance with an exemplary embodiment of the invention, a method of selecting a gauge molecule to be added to a screening library, comprising:

providing a set of chemical molecules and at least a part of a screening library;

selecting a potential gauge molecule from said set of chemical molecules;

25   determining a rigidity of said potential gauge molecule; and

rejecting said potential gauge molecule responsive to a lack of rigidity of said gauge molecule. Optionally, said lack of rigidity is absolute. Alternatively, said lack of rigidity is relative to other potential scaffolds.

In an exemplary embodiment of the invention, the method comprises:

30   determining a spanning, in chemical configuration space, of said part of a screening library;

determining at least one spatial chemical configuration of said potential molecule; and

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selecting said potential gauge molecule if it adds at least one significant spatial chemical configuration to said screening library.

Optionally, providing a set of molecules comprises generating said molecules using a single scaffold to which moieties are selectively attached. Alternatively or additionally,

5   providing a set of molecules comprises providing a chemical library.

In an exemplary embodiment of the invention, said gauge is selected if it adds at least one spatial chemical configuration not previously provided or overlapping a provided configuration.

There is also provided in accordance with an exemplary embodiment of the invention,

10   a method of creating at least a portion of a screening library, comprising:

selecting a scaffold molecule to which moieties can be added;

determining a plurality of potential gauges which can be created by attaching moieties to said scaffold; and

selecting a subset of said gauges that do not substantially overlap in chemical

15   configurations. Optionally, the method comprises rejecting potential gauges that add over six spatial chemical configurations.

There is also provided in accordance with an exemplary embodiment of the invention, a method of reducing a screening library, comprising:

for each molecule in at least part of said library, determining substantially all the spatial

20   chemical configurations of a certain order of binding points provided by the molecule; and

removing a plurality of molecules which add redundant spatial chemical configurations. Optionally, said certain order is three.

There is also provided in accordance with an exemplary embodiment of the invention, a method of reducing a screening library, comprising:

25   for each molecule in at least part of said library, calculating a binding probability of said molecules based on energetic considerations; and

removing at least some molecules whose binding probability is below a threshold value. Optionally, said binding probability is calculated using a formula which is inversely dependent on a flexibility of the molecule. Alternatively or additionally, said binding

30   probability is at least estimated based on a solubility of the molecule.

There is also provided in accordance with an exemplary embodiment of the invention, a method of designing a screening library for a projected target molecule task, comprising:

determining a desired range of distances between binding points to be directly identified by said library;

determining a desired overlap between measures provided by gauge molecules of said library;

determining a set of desired binding types to be discriminated between; and

generating a plurality of gauges, said gauges each defining a plurality of binding types and distances between them, such that said gauges cover a spatial chemical configuration space that includes said distances and said binding types with said desired overlap. Optionally, generating a plurality of moieties comprises generating by attaching moieties to scaffolds. Alternatively or additionally, said gauges cover a spatial chemical configuration space of triplets of binding points. Alternatively or additionally, said projected target molecule task comprises proteins.

In an exemplary embodiment of the invention, said overlap is at least two. Alternatively said overlap is at least four. Alternatively, said overlap is at least six.

In an exemplary embodiment of the invention, said gauges are substantially rigid. Alternatively or additionally, said coverage takes into account an inherent flexibility of binding.

In an exemplary embodiment of the invention, generating comprises generating substantially same configurations by different gauges, thereby providing at least part of said overlap. Optionally, generating comprises providing a repetition factor of at least two.

In an exemplary embodiment of the invention, generating comprises generating substantially different configurations by different gauges, which different configurations overlap due to a degree of flexibility thereof, thereby providing at least part of said overlap.

In an exemplary embodiment of the invention, the method comprises generating a set of drug leads for said target based on said information. Optionally, the method comprises removing known drug leads for said target from said set.

There is also provided for in accordance with an exemplary embodiment of the invention, a lead set produced by one of the methods described above.

There is also provided in accordance with an exemplary embodiment of the invention, a drug lead comprising:

a plurality of substantially rigid scaffolds molecule sections;

at least one link interconnecting said scaffold molecule sections; and

a plurality of moieties attached to said scaffolds.

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There is also provided in accordance with an exemplary embodiment of the invention, a screening library comprising:

at least 10,000 molecules generated by attaching moieties to a set of fewer than 50 scaffold molecules. Optionally, fewer than 20 scaffold molecules are used to generate said at

5   least 10,000 molecules. Alternatively or additionally, said scaffolds include at least one of the following scaffold molecules: Thiophene; 1H-Pyrrole; Furan; Benzene; Pyridine; Pyrimidine; Pyrazine; 6H-Thieno[2,3-b]pyrrole; 1,6-Dihydro-pyrrolo[2,3-b]pyrrole; 1H-Indole; Thieno[2,3-d]pyrimidine; 6,7-Dihydro-pyrazolo[1,5-a]pyrimidine; Quinoline; Isoquinoline; Quinoxaline;   3,4-Dihydro-benzo[e][1,4]diazepin-5-one;   3,8-Dihydro-4H-pyrrolo[2,3-

10   e][1,4]diazepin-5-one;   3,4-Dihydro-thieno[2,3-e][1,4]diazepin-5-one;   3,6-Dihydro-4H-pyrrolo[3,2-e][1,4]diazepin-5-one;   5H,11H-Dibenzo[b,f][1,5]diazocine-6,12-dione;   1,4-Dihydro-10H-1,4,10-1,4,10-triaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione;   4H,10H-1-Thia-4,10-diaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione;   Dipyrrolo[1,2-c;2',1'-e]imidazol-5-one;   1,4,7,9-Tetrahydro-1,4,6,9-tetraaza-dicyclopenta[a,e]cyclooctene-5,10-

15   dione;   4,7,9-Trihydro-1-thia-4,6,9-triaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 2,4,9,Trihydro-11lambda*4*,6-dithia-4,9-diaza-dicyclopenta[a,e]cyclooctene-5,10-dione;   6,9-Dihydro-5H-1-thia-5,8,9,triaza-cyclopenta[a]azulen-4-one;   3,10,Dihydro-4H-[1,4]diazepino[5,6-b]indol-5-one;   3,6-Dihydro-4H-[1,4]diazepino[6,5-b]indol-5-one;   7,8-Dihydro-1H-1,7,10-triaza-cyclohepta[e]inden-6-one;   8,9-Dihydro-3H-3,6,9-triaza-

20   cyclohepta[e]inden-10-one;   7,8-Dihydro-1H-1,5,8-triaza-cyclohepta[f]inden-9-one;   8,9-Dihydro-5,6,9,11-tetraaza-cyclohept[b]naphthalene-10-one;   3,4-Dihydro-[1,4]diazepino[5,6-b]quinolin-5-one;   8,9-Dihydro-4,8,11-triaza-cyclohepta[a]naphthalene-7-one;   11H-10,11-Diaza-benzo[b]fluorine; α-hydroxyacids; α-aminoacids; cohels; Bicyclo[2.2.2]octane; 2-Methylene-2,3-dihydrobenzo[1,4]dioxine;   6,7-Dihydro-2H-pyrazino[1,2-a]pyramidine;   9H-

25   Fluorene;   1,4-Diaza-bictclo[2.2.2]octane;   1-Aza-bicyclo[2.2.2]octane;   Pyrido[2,3-d]pyrimidine;   5-Methylene-1,5-dihydro-pyrrol-2-one;   Bezno[4,5]imidazo[1,2-a]pyrimidine; 1,4-Dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine; 4,10-Dihydro-1,4a,10-triaza-phenanthren-9-one;   1,5-Dihydro-imidazo[1,2-a]pyrimidin-2-one;   1,2,3,5-Tetrahydro-imidazo[1,2-a]pyrimidine;   Thiazolo[3,2-a]thieno[2,3-d]pyrimidin-5-one;   1,9-Dithia-4a,10-diaza-

30   cyclopenta[b]fluoren-4-one;   5,6-Dihydro-1-thia-5,7,8,9a-tetraaza-cyclopenta[e]azulen-4-one; 6,10-Dihydro-5H-1-thia-5,7,10a-triaza-benzo[e]azulen-4-one;   4,5-Dihydro-3-thia-4,5a,10-triaza-cyclopenta[a]fluorine;   8H-1-Thia-cyclopenta[a]indene;   3-Thia-4,5a,10-triaza-cyclopenta[a]fluorine; 6,7,9,11-Tetrahydro-10-thia-6,9-diaza-indeno[1,2-a]azulene-5,8-dione;

2,3,6,7,12a-Hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione;   5,10-Dihydro-4H-
2,3a,10-triaza-cyclopenta[a]fluorine;   5H-Pyrido[4,3-b]indole;   11H-Indolizino[1,2-b]quinolin-
9-one;   1,2-Dihydro-2,4a,9,-triaza-anthracene-3,10-dione;   6H-Isoindolo[2,1-a]indole;   1,5-
Dihydro-benzo[b][1,4]diazepin-2-one;   5,10-Dihydro-dibenzo[b,e][1,4]diazepin-11-one;   5,11-
Dihydro-benzo[e]pyrido[3,2-b][1,4]diazepin-6-one;   4,9-Dihydro-3-thia-4,9-diaza-
benzo[f]azulen-10-one;   Benzo[g]quinoxaline;   Pyrazino[2,3-b]quinoxaline;   Pyrido[2,1-
b]quinazolin-11-one;   1-Thia-4a,9-diaza-cyclopenta[b]naphthalene-4-one;   2-Methylene-4H-
benzo[1,4]thiazin-3-one.

In an exemplary embodiment of the invention, at least 4 of said scaffolds have exactly a
single ring. Alternatively or additionally, at least 4 of said scaffolds have exactly two rings.
Alternatively or additionally, at least 4 of said scaffolds have exactly three rings. Alternatively
or additionally, at least 4 of said scaffolds have exactly four rings. Alternatively or
additionally, said library includes at least 50,000 thus generated molecules. Alternatively or
additionally, said library includes at least 100,000 thus generated molecules.

In an exemplary embodiment of the invention, said scaffolds include at least three of
said following scaffold molecules. Alternatively or additionally, said scaffolds include at least
ten of said following scaffold molecules.

In an exemplary embodiment of the invention, said generated molecules are
substantially rigid. Alternatively or additionally, said molecules span a configuration space of
spatial geometrical patterns of binding point types, including at least 25% of the patterns that
exist in protein targets. Optionally, said molecules span at least 50% of the patterns.

In an exemplary embodiment of the invention, said molecules span a space defining at
least 4 distinct binding point chemistry types.

In an exemplary embodiment of the invention, said molecules span a space defining at
least 5 distinct binding point chemistry types.

There is also provided in accordance with an exemplary embodiment of the invention,
a screening library, comprising:

at least 100 gauge molecules generated by attaching moieties to at least one of the
following scaffolds: Thiophene; 1H-Pyrrole; Furan; Benzene; Pyridine; Pyrimidine; Pyrazine;
6H-Thieno[2,3-b]pyrrole;   1,6-Dihydro-pyrrolo[2,3-b]pyrrole;   1H-Indole;   Thieno[2,3-
d]pyrimidine; 6,7-Dihydro-pyrazolo[1,5-a]pyrimidine; Quinoline; Isoquinoline; Quinoxaline;
3,4-Dihydro-benzo[e][1,4]diazepin-5-one;   3,8-Dihydro-4H-pyrrolo[2,3-e][1,4]diazepin-5-one;
3,4-Dihydro-thieno[2,3-e][1,4]diazepin-5-one;   3,6-Dihydro-4H-pyrrolo[3,2-e][1,4]diazepin-5-

one; 5H,11H-Dibenzo[b,f][1,5]diazocine-6,12-dione; 1,4-Dihydro-10H-1,4,10-1,4,10-triaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione; 4H,10H-1-Thia-4,10-diaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione; Dipyrrolo[1,2-c;2',1'-e]imidazol-5-one; 1,4,7,9-Tetrahydro-1,4,6,9-tetraaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 4,7,9-Trihydro-1-thia-4,6,9-triaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 2,4,9,Trihydro-11lambda*4*,6-dithia-4,9-diaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 6,9-Dihydro-5H-1-thia-5,8,9,triaza-cyclopenta[a]azulen-4-one; 3,10,Dihydro-4H-[1,4]diazepino[5,6-b]indol-5-one; 3,6-Dihydro-4H-[1,4]diazepino[6,5-b]indol-5-one; 7,8-Dihydro-1H-1,7,10-triaza-cyclohepta[e]inden-6-one; 8,9-Dihydro-3H-3,6,9-triaza-cyclohepta[e]inden-10-one; 7,8-Dihydro-1H-1,5,8-triaza-cyclohepta[f]inden-9-one; 8,9-Dihydro-5,6,9,11-tetraaza-cyclohept[b]naphthalene-10-one; 3,4-Dihydro-[1,4]diazepino[5,6-b]quinolin-5-one; 8,9-Dihydro-4,8,11-triaza-cyclohepta[a]naphthalene-7-one; 11H-10,11-Diaza-benzo[b]fluorine; α-hydroxyacids; α-aminoacids; cohels; Bicyclo[2.2.2]octane; 2-Methylene-2,3-dihydrobenzo[1,4]dioxine; 6,7-Dihydro-2H-pyrazino[1,2-a]pyramidine; 9H-Fluorene; 1,4-Diaza-bictclo[2.2.2]octane; 1-Aza-bicyclo[2.2.2]octane; Pyrido[2,3-d]pyrimidine; 5-Methylene-1,5-dihydro-pyrrol-2-one; Bezno[4,5]imidazo[1,2-a]pyrimidine; 1,4-Dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine; 4,10-Dihydro-1,4a,10-triaza-phenanthren-9-one; 1,5-Dihydro-imidazo[1,2-a]pyrimidin-2-one; 1,2,3,5-Tetrahydro-imidazo[1,2-a]pyrimidine; Thiazolo[3,2-a]thieno[2,3-d]pyrimidin-5-one; 1,9-Dithia-4a,10-diaza-cyclopenta[b]fluoren-4-one; 5,6-Dihydro-1-thia-5,7,8,9a-tetraaza-cyclopenta[e]azulen-4-one; 6,10-Dihydro-5H-1-thia-5,7,10a-triaza-benzo[e]azulen-4-one; 4,5-Dihydro-3-thia-4,5a,10-triaza-cyclopenta[a]fluorine; 8H-1-Thia-cyclopenta[a]indene; 3-Thia-4,5a,10-triaza-cyclopenta[a]fluorine; 6,7,9,11-Tetrahydro-10-thia-6,9-diaza-indeno[1,2-a]azulene-5,8-dione; 2,3,6,7,12a-Hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione; 5,10-Dihydro-4H-2,3a,10-triaza-cyclopenta[a]fluorine; 5H-Pyrido[4,3-b]indole; 11H-Indolizino[1,2-b]quinolin-9-one; 1,2-Dihydro-2,4a,9,-triaza-anthracene-3,10-dione; 6H-Isoindolo[2,1-a]indole; 1,5-Dihydro-benzo[b][1,4]diazepin-2-one; 5,10-Dihydro-dibenzo[b,e][1,4]diazepin-11-one; 5,11-Dihydro-benzo[e]pyrido[3,2-b][1,4]diazepin-6-one; 4,9-Dihydro-3-thia-4,9-diaza-benzo[f]azulen-10-one; Benzo[g]quinoxaline; Pyrazino[2,3-b]quinoxaline; Pyrido[2,1-b]quinazolin-11-one; 1-Thia-4a,9-diaza-cyclopenta[b]naphthalene-4-one; 2-Methylene-4H-benzo[1,4]thiazin-3-one.

Optionally, said molecules are generated using at least one of the following scaffolds:
Thiophene; 1H-Pyrrole; Furan; Benzene; Pyridine; Pyrimidine; Pyrazine; 6H-Thieno[2,3-b]pyrrole; 1,6-Dihydro-pyrrolo[2,3-b]pyrrole; 1H-Indole; Thieno[2,3-d]pyrimidine; 6,7-

Dihydro-pyrazolo[1,5-a]pyrimidine; Quinoline; Isoquinoline; Quinoxaline; 3,4-Dihydro-benzo[e][1,4]diazepin-5-one; 3,8-Dihydro-4H-pyrrolo[2,3-e][1,4]diazepin-5-one; 3,4-Dihydro-thieno[2,3-e][1,4]diazepin-5-one; 3,6-Dihydro-4H-pyrrolo[3,2-e][1,4]diazepin-5-one; 5H,11H-Dibenzo[b,f][1,5]diazocine-6,12-dione; 1,4-Dihydro-10H-1,4,10-1,4,10-triaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione; 4H,10H-1-Thia-4,10-diaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione; Dipyrrolo[1,2-c;2',1'-e]imidazol-5-one.

In an exemplary embodiment of the invention, said at least 100 molecules comprise at least 300 molecules. Alternatively or additionally, said at least 100 molecules of said library are generated using a single one of said scaffolds.

There is also provided in accordance with an exemplary embodiment of the invention, a screening library comprising a set of at least 10,000 substantially rigid molecules. Optionally, said set comprises at least 50,000 substantially rigid molecules. Alternatively or additionally, said set comprises at least 100,000 substantially rigid molecules.

In an exemplary embodiment of the invention, said set is selected to have a an expected binding rate of at least 0.1% of the library for protein targets in general. Optionally, said expected binding rate is at least 0.5%.

In an exemplary embodiment of the invention, said set is designed to provide molecules with a uniformity of hit probability for a generalized target of within a ratio of 1:100 for the whole set. Optionally, said ratio is within 1:10.

In an exemplary embodiment of the invention, said set spans a space of spatial chemical configurations, each such configuration defining a certain plurality of binding points having distances between them, the set covering substantially all possible configurations in the space in a given range of distances.

There is also provided in accordance with an exemplary embodiment of the invention, a screening library, comprising:

a plurality of at least 5,000 gauge molecules, each such molecule defining at least one spatial configuration of binding type points,

wherein substantially each point in a space of such configurations is covered by at least two different gauge molecules. Optionally, each point is covered by at least two substantially identical spatial configurations. Alternatively or additionally, each point is covered by at least two substantially different spatial configurations. Alternatively or additionally, said space is a space of triangles defined by binding type at vertexes and distances between vertexes. Optionally, said space includes distances of between 4 Å and 8 Å (angstrom $= 10^{-10}$ meters).

Alternatively or additionally, said space includes distances of between 2 Å and 10 Å. Alternatively or additionally, said space includes at least 5 different binding types. Optionally, said space includes at least 7 different binding types.

In an exemplary embodiment of the invention, said space includes omni-directional binding types. Alternatively or additionally, said space includes directional binding types.

In an exemplary embodiment of the invention, said substantially each point in said space is covered by at least three gauges.

In an exemplary embodiment of the invention, substantially all the gauges include a plurality of configurations of said space.

There is also provided in accordance with an exemplary embodiment of the invention, a method of obtaining information about a binding behavior of a target molecule, comprising:

providing a set of substantially rigid chemical gauges, a significant number of said gauges being expected to bind with said target;

reacting said target with a plurality of gauges of said set of gauges; and

physically analyzing a structure of said target bound to a gauge. Optionally, physically analyzing comprises analyzing using NMR. Alternatively or additionally, physically analyzing comprises analyzing using X-ray crystallography. Alternatively or additionally, physically analyzing comprises analyzing using binding with a set of gauges. Alternatively or additionally, the method comprises virtually super-imposing a plurality of structures obtained by said physically analyzing.

There is also provided in accordance with an exemplary embodiment of the invention, a method of constructing a lead, comprising:

providing a set of substantially rigid chemical gauges;

reacting said target with a plurality of gauges of said set of gauges;

assaying a binding of said gauges with said target to obtain a plurality of assay results; and

constructing a lead based on said assay results. Optionally, constructing a lead comprises linking together a plurality of gauges found to bind in said assaying. Alternatively or additionally, constructing a lead comprises modifying an existing molecule to have moieties that correspond to binding locations found by said assaying.

BRIEF DESCRIPTION OF THE DRAWINGS

Non-limiting embodiments of the invention will be described with reference to the following description of exemplary embodiments, in conjunction with the figures. The figures

are generally not shown to scale and any measurements are only meant to be exemplary and not necessarily limiting. In the figures, identical structures, elements or parts which appear in more than one figure are preferably labeled with a same or similar number in all the figures in which they appear, in which:

Fig. 1 is a schematic diagram of a target protein including a plurality of binding points;

Fig. 2 is a flowchart of a method of drug discovery, in accordance with an exemplary embodiment of the invention;

Fig. 3 is a flowchart of a method of target measurement, in accordance with an exemplary embodiment of the invention;

Fig. 4A is a schematic illustration of an exemplary gauge, in accordance with an exemplary embodiment of the invention;

Fig. 4B shows the gauge of Fig. 4A, interacting with the target protein of Fig. 1;

Fig. 5 is a flowchart of a method of determining which triangles did bind to a target, in accordance with an exemplary embodiment of the invention;

Fig. 6A is a flowchart of a method of determining a spatial layout of binding locations from the results of the method of Fig. 5, in accordance with an exemplary embodiment of the invention; and

Fig. 6B is a flowchart of an alternative method of determining a spatial layout of binding locations from the results of the method of Fig. 5, in accordance with an exemplary embodiment of the invention.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

1. OVERVIEW

The high specificity of many biological molecules, such as enzymes, is created by the existence, in such a molecule, of a particular spatial arrangement of binding locations. It is believed that for a substrate molecule to succeed in usefully interacting with the enzyme, it must match (at least part of) the particular spatial arrangement. In the pharmaceutical industry, this specificity can be utilized by finding small molecules that mimic the shape and chemical affinities of the substrate molecule. In a typical drug discovery method, such a small molecule is found by trying out millions of small molecules and, once finding a molecule which appears to have some affinity, chemically fine tuning that "lead" until a better binding is found. In an exemplary embodiment of the invention, the particular spatial arrangement is mapped and this map is used to assist in the drug discovery process and, ultimately, in finding new and useful small molecule drugs. It should be noted that, in general, the spatial geometry of the binding locations is three dimensional.

In the following description, the molecule is called a target and the spatial arrangement is called a target area or a pharmacophore. However, as will be clear, a mapping method in accordance with an exemplary embodiment of the invention and/or its derivatives have uses beyond drug discovery, for example, developing herbicides and targeted anti-bodies. Thus, the

terms used are used for convenience and not for limiting the desired coverage, except where noted otherwise.

Fig. 1 is a schematic diagram of a target protein 100 including a plurality of binding locations 102 (and 108). As shown, binding locations 102 are arranged in a target area 104,

5   which is designed to accept the substrate of the protein. In some proteins, a target area of interest is a control area 106 of the protein (with binding locations 108), which, when bound, changes the behavior of the protein (e.g., changing the configuration of the substrate receiving area of the protein). Possibly, a plurality of non-functional binding locations 110 are found on the outside of the protein.

10 Although the following description focuses on finding small molecules for affecting enzymatic proteins, target 100 may be any bio-molecule whose biological behavior may be desirably affected by the binding of a molecule to it. For example, target 100 may be one or more of DNA, RNA, signaling proteins such as hormones, structural hormones, growth factors, other proteins, anti-bodies, cell receptors, ion channels, cytokines, complexes,

15 membranes, toxins (biological and synthetic), small and large molecule drugs and carbohydrates. Non-biological application are also envisioned, for example for assessing enzymes used for washing and industrial uses. In addition, the searched-for molecule need not be a small molecule, for some applications, for example, it may be a peptide, protein, antibody or metal complex.

20 In accordance with some exemplary embodiments of the invention, the mapping of target area 104 (or 106) is provided by making multiple geometrical and/or chemical affinity measurements of the target area and then correlating the measurements to provide a three dimensional model of target area 104. In an exemplary embodiment of the invention, the measurements are made using a set of selective gauge molecules. In an exemplary embodiment

25 of the invention, the gauges are selective to certain bond geometries and/or certain chemical affinities, with an optional small range of flexibility. In a set of gauges a large range of geometries, sizes and/or affinities is optionally provided using a larger number of specific gauges.

In an exemplary embodiment of the invention, each gauge molecule makes multiple

30 measurements simultaneously and there is an overlap between the measurements made by different gauge molecules. A processing step is optionally provided in which the composite measurement from gauges are inter-related to yield an indication of individual measurements which are then used for reconstructing a three-dimensional map. Additional side information is

optionally used for the processing and/or or for analyzing and/or using the results of the processing. Various examples of such side information are described below.

2. EXEMPLARY PROCESS OF DRUG DISCOVERY

5

Fig. 2 is a flowchart of a method of drug discovery 200, in accordance with an exemplary embodiment of the invention. At 202, a target 100 for which a drug is to be developed, is provided. Optionally, at 204, a subset of gauges is selected for the measurement of target 100. Alternatively, a single set of gauges is used for all targets.

At 206, the gauges are used to measure the spatial layout of interaction locations 102 and/or 108.

10

At 208, a model of at least part of the active and/or control areas of target 100 is reconstructed from the measurements. At 210 and 212 one or more molecules that match the measurements are determined. At 214, the matching molecules are further processed to provide drugs.

Further details of this method are described below. Alternative methods are also

15

described below.

3. DETAILS OF PROCESS

3.1 TARGET MEASUREMENT

Fig. 3 is a flowchart of a method of target measurement 300, in accordance with an exemplary embodiment of the invention. At 302, an amount of target 100 and one or more

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gauges are combined in a container, and possibly allowed to incubate (304) so that gauges can bind to interaction locations in target 100. In some embodiments of the invention, the target is also incubated with a substrate or another molecule. Such incubation may be provided for various reasons, for example, to force a conformal change on the target to assist in dissolving, to keep the target alive and/or as part of a functional assay. The target may be in a relatively

25

pure state, for example a purified replicated DNA segment. Alternatively, the target may be provided in a more natural environment, for example in a living cell or with associated molecules (e.g., whose interactive effects may be unknown). Optionally, a plurality of overlapping gauges (i.e., overlapping in them being able to measure same or similar spatial geometries) are incubated together in a same assay.

30

At 306, the degree of binding of the gauge to target 100 is optionally determined. The method used may depend on the type of assay used, various examples of which are provided below. Alternatively or additionally, at 308, an effect on the function of target 100 is determined, various examples are provided below.

It should be noted that assays suitable for detecting binding of a test molecule to a target molecule are well known for drug discovery and many are suitable for the present invention, possibly with no modification.

The assaying process may then be repeated with a different gauge and/or different

5   conditions (310), such as solvent, temperature and pH. Varying the conditions may be used, for example, to determine the strength of the binding and/or to compensate for unavailable gauges, for example by forcing conformal changes on target 100. The repetition may depend on preliminary binding results for one or more gauges and/or may depend on preliminary measurements or measurement failures.

10   In an exemplary embodiment of the invention, the assays are at a 1-100 micro Molar concentration of the gauge. However, other concentrations may be used. The concentration may depend, for example, on the solubility of the gauge and/or various toxic or other effects associated with the gauge. In many cases, the concentrations used will depend on the sensitivity of the assay.

15   The purity of the target may or may not be important, for example, depending on the affinity of the gauge to the impurities and/or on the sensitivity of the assay to the impurities.

4. EXEMPLARY ASSAYS

4.1 FUNCTIONAL ASSAY

Many types of functional assaying methods are known in the art. In general, the treated

20   target is provided with its normal substrate (for proteins) and a measurement of enzymatic activity is used to determine the functional effect of the gauge, relative to a baseline or a control portion of material. Automated parallel assay devices, such as manufactured by Tecan (Switzerland), Zymark (USA) or Cybio (DE) can perform multiple functional assays in parallel, for example, for different gauges and/or for better statistics on a single gauge-target

25   match.

Functional assays may be on various levels, for example, on a molecular, cellular or organism level. In general, any known functional assay may be used to assay the functionality of a gauge.

In an exemplary embodiment of the invention, the gauge acts like a ligand of the target

30   and compete or otherwise affects the functionality of the target. These effects may be of various types, for example, the gauge may bind where the normal substrate is supposed to bind, the gauge may bind near where the substrate binds, but still block the substrate from binding, the gauge may bind in a way that does not block the substrate but would, if the gauge

were larger (suitable for a binding assay) and/or the gauge may be agnostic rather than antagonistic in its behavior, enhancing the affinity of the target for the substrate.

DNA targets can be assayed, for example, using replication methods (e.g., to see if replication is inhibited or enhanced). Alternatively, DNA targets are assayed by determining

5   their interaction with DNA chips after the test binding. Such DNA chips typically include a substrate on which a plurality of short DNA segments are mounted in a known pattern, with the segments selected to bind (e.g. be specific and complementary) to portions of a searched for DNA sequence and/or match sections of a non-linear DNA segment. It is expected that the type and/or relative frequencies of bindings to various short DNA segments on a DNA chip

10   depend on the degree and/or location of binding of a gauge to a DNA molecule. For example, a gauge may block a certain part of a DNA molecule from matching up with a DNA chip segment. In another example, a gauge may force a conformal change in a DNA molecule, which change will interfere with binding with one DNA chip segment but which may allow binding with a previously unsuitable DNA chip segment.

15   *4.2 BINDING ASSAY*

In a binding assay, the binding of a gauge to a target is directly measured. It should be noted, however, that a binding assay may be less indicative than a functional assay, as a gauge can bind at a location outside of the target area and provide no useful information about the target area. In addition, the sensitivity of a binding assay may be lower, since the detection

20   sensitivity of binding is usually lower and typical binding rates are also quite low. However, in some cases, a functional assay cannot be performed, for example if the gauge interacts with the substrate, or if a target function is not known, or may be difficult or time consuming to perform, for example if the assay requires a living cell. Also, a gauge may bind in an active area without this binding affecting the functionality, as measured by a particular functional

25   assay.

Various types of binding assays are known in the art and may be used, for example as described in the Handbook of Drug Screening, edited by Ramakrishna Seethala and Prabhavathi B. Fernandes, in Drugs and the Pharmaceutical Sciences, Volume 114, New York, NY, Marcel Dekker, 2001, the disclosure of which is incorporated herein by reference.

30   Both functional assays and binding assays may be performed in many ways, the current technology being robotic performance of tests and the emerging technology being flow-through analysis (e.g., using DNA chips). It should be noted that 100,000 test systems are becoming available, which means that in some embodiments of the invention, screening using

a gauge library can be completed in one step (day). Optionally, this is used to prevent the need to clean out gauge delivery systems between screening targets.

In some embodiments of the invention, the binding assay (of a functional assay) includes modifying a gauge, for example, attaching a fluorescent material to the gauge.

5   Depending on the attachment point, this may cause conformal changes in some of the gauges and/or cause steric clashes. It is expected that the overlap between gauges will overcome this problem, at least in a significant number of cases.

In other embodiments of the invention, the gauges are not changed, or are changed in non-material ways. For example, for an NMR binding assay or an x-ray crystallography

10 binding assay no change is required. In a radioactivity based assay, radioactive isotopes can be used in the gauges. In an exemplary embodiment of the invention, non-radioactive isotopes (half spin isotopes) are used in producing the gauges, to provide binding detection and/or better analysis of NMR data. In these assays, unbound gauges may be separated from the targets, for example, using methods known in the art, for example, if the target is bound to a

15 surface, washing will remove unbound gauges.

In some embodiments of the invention, the binding of the gauge has a non-functional effect on the target, which may be detected or measured, for example, affecting a vibration frequency of a fluorescent tail attached to the gauge or the target. In an exemplary embodiment of the invention, the gauge binds with the target in a manner similar to that of a ligand of the

20 target. Various techniques, for example as known in the art (e.g., NMR, IR) may be used to analyze the combined target/gauge structure. Optionally, once a binding gauge or other substrate is found, a gauge set is used to measure the combined target/ligand structure.

In some binding assays, a plurality of differently marked gauges may be assayed simultaneously and possibly differentially, for example, by a attaching a different florescent

25 marker to different gauge used together and/or using different radioactive isotopes for different gauges.

Optionally, the binding assay (and/or a functional assay) may include changing various environmental parameters, such as temperature, pH and/or other environmental variables, for example to determine a strength of binding.

30 In an exemplary embodiment of the invention, a binding assay is used to determine a baseline level of binding of the gauge outside active areas of the target. In one example, the degree of binding of a particular gauge to alpha helixes in a protein may be known from an

analog of the target. The total binding to the target, however, includes bindings to non-helix parts of the protein and/or target areas of the target.

In an exemplary embodiment of the invention, it is noted that a large number of hits are expected and/or an overlap between gauges is provided. As a result, lower quality and/or faster assays are used, since noise caused by low binding rates may be less of a problem. In one example, borderline results form two assays are combined, based on a repetition of triangular measures between the gauges used in the assays.

5. GAUGES, GENERAL

5.1 EXEMPLARY GAUGE

Fig. 4A is a schematic illustration of an exemplary gauge 400, in accordance with an embodiment of the invention.

Gauge 400 comprises a scaffold 402 and four chemical moieties 406, 410, 414 and 422 attached to scaffold 402 via bonds 404, 408, 412 and 420, respectively. This is only an exemplary gauge, as the properties of all of these elements may vary, for example as described below. In particular, one or more of the type of moiety, number of moieties, type of bond, distance between moiety and scaffold, type of scaffold and location of connection to the scaffold may be varied for different gauges, sets of gauges and/or embodiments of the invention.

In an exemplary embodiment of the invention, a plurality of moieties cooperate to define a measure. In an exemplary embodiment of the invention, the gauge purpose is to detect interaction locations that bind to those moieties that define a measure at the distances between the moieties. The matching of a measure to the target molecule may be indicated by the binding of the gauge. In an exemplary embodiment of the invention, a basic unit of measure is a triangle (or other geometric shape) defined by a subset of all the moieties. As will be described below, the shape of a triangle has particular properties which make it suitable for some embodiments. In general, if a gauge includes more than the number of moieties in a measure (e.g., more than two moieties for a linear measure, more than three for a triangle), more than one measure may be provided by a single gauge. Thus, in the exemplary embodiment of the invention shown, a plurality of different triangle measures are defined in a single gauge. In some embodiments and in some cases, a gauge will include only one measure, for example, gauge 400 includes only a single four-point measure, but four triangle measures. Exemplary methods of determining which of various possible measures actually bound, are described below.

One triangle geometry is shown by dashed lines 416, 418 and 420 that define the distances between pairs of moieties of gauge 400. As noted above, in an exemplary embodiment of the invention, the gauge purpose is to detect interaction locations that bind to those moieties (406, 410, 414) at the distances defined by dashed lines 416, 418 and 420 (e.g., triangle sides). Assuming gauge 400 included only moieties 406, 410 and 414, then a binding of gauge 400 to target 100 can be is used as an indication that three interaction sites, of a type suitable to bind to moieties 406, 410 and 414 are approximately at the respective distances defined by gauge 400. Since gauge 400 defines multiple triangles, a binding of gauge 400 indicates that at least one of the triangles defined by the moieties, binds.

Fig. 4B shows gauge 400, interacting with target 100, at three interaction locations 450, 452 and 454. Non-interacting moieties and the rest of the gauge are not shown.

5.2 NUMBER OF MOIETIES IN A MEASURE

As noted, each plurality of moieties defines a measures. While the present invention accommodates, in some embodiments thereof measures, with two, three, four and/or other numbers of moieties and/or gauge sets including a mixture of different measures, in an exemplary embodiment of the invention, the basic measure used is a triangle, with three moieties. Using a triangle may provide one or more of the following potential benefits:

(a) A triangle defines a stable spatial relationship, which may be useful as a unit component when "constructing" a model in three dimensions of the target area, from the binding results.

(b) There are fewer possible triangles than four-sided measures (for example). Thus, generating a library that includes measures that cover an entire space is less time consuming. Further, as it is desirable in some embodiments of the invention to provide overlap between measures, such overlapping measures are more easily provided if there are fewer measures. It is possible that chemical limitations may prevent the construction of high-order measure gauge libraries.

(c) A triangle always lies in a plane (e.g., three points define a plane), which may be mathematically useful for some reconstruction methods.

(d) For some applications, a triangle represents the lowest number of binding points that will result in a measurable binding to a target active area. A typical drug includes six or more binding points, often as many as ten or more. Conversely, a higher-order measure may bind too strongly. In other applications, the optimal number of moieties in a measure may be higher or lower, of course.

34

Alternatively, a measure including two moieties are used, for example, defining lines. Alternatively or additionally, four- or higher valance measures are used, for example, to define more uniquely an interaction location configuration. In some embodiments of the invention, a mix of different valance measures may be used, in the gauge set and/or in the reconstruction,

5   for example, 2-point, 3-point, 4-point and 5-point measures, which may or may not be planar.

5.3 NUMBER OF MOIETIES IN A GAUGE

In an exemplary embodiment of the invention, the number of moieties in a gauge is between four and ten, however, a smaller (e.g., three) or greater number may be provided. Some scaffolds may be limited in the number of different moieties, moiety positions and/or

10   moieties combinations possible. Larger numbers of moieties are generally desirable if the moieties define different triangle measures. Conversely, gauges with multiple attachment points and/or gauges with many moieties may be more prone to steric clashes and/or other adverse interactions between the moieties, which inhibit binding.

While the scaffold itself has chemical properties and may be considered as having

15   moieties, in some embodiments of the invention, these properties are ignored, for example during library design and/or during binding results analysis. Alternatively, the properties of the scaffold may be considered, for example only during analysis and/or during library design.

5.4 MOIETY TYPES

In an exemplary embodiment of the invention, the moieties are selected to reflect the

20   types of bonds that the drug is expected to make with the target. In an exemplary embodiment of the invention, the moieties are selected based on their chemical behavior. If a particular behavior is exhibited by several moieties, in an exemplary embodiment of the invention, only a smallest one of the moieties is selected. In some embodiments of the invention, multi-purpose moieties, which can bind to several different binding sites, are used instead of moieties which

25   can only bind to one type of target site. The specificity of the moieties selected may depend, for example, on the total number of moieties, their size and their amenability for chemical processing. It should be noted that some of the moieties are directional, while others are non-directional. Where available, non-directional bonds may be preferred over directional bonds. In some exemplary embodiments of the invention, two levels of measurement are performed, a

30   coarse resolution level and a fine resolution level. More specific moieties may be used during the fine resolution level of measurement. Additional details and methods for optionally

reducing the number of moieties used in some embodiments of the invention, are described below.

Following is a list of moieties of which one or more may be attached to gauges:

a. Hydrogen bond donor. Directional bond.

b. Hydrogen bond acceptor. Directional bond

c. Positive charge. Non-directional bond.

d. Negative charge. Non-directional bond.

e. Aromatic ring. Directional bond.

f. Hydrophobic group. Non-directional in general, however, some, e.g., rings, may be directional with a preferred direction perpendicular to the ring plane.

Different moieties may be used in other embodiments of the invention, for example, also providing one or more of Halogen, Carbonyl, Phosphate and Sulfate bonds. It should be noted that the different moieties may differ greatly in the their chemical affinities or they may differ less or even slightly. In some exemplary gauge sets, the slight difference between moiety affinities is used to fine tune a measurement distinction between bond types.

With respect to the directional bonds, in some embodiments of the invention, it is assumed that the bond has sufficient spatial flexibility so that a small number, e.g., seven, different directional bonds will suffice to cover all the possible bond directions. Alternatively, smaller or greater numbers of bond directions may be used. Optionally, different directional bonds have different numbers of directions represented in a gauge library. The angular distribution of the directions may be, for example uniform, or it may be non-uniform, for example depending on the bond type.

Several different sizes of hydrophobic bonds may exist. In an exemplary embodiment of the invention, two sizes are selected and represented by different moieties. An aromatic ring may also serve, as an oversized hydrophobic moiety. Alternatively or additionally, an aromatic ring is used to match aromatic bonds with other rings and/or some types of hydrogen bonds.

The above selection of moieties and directions results in 25 unique moieties, which can be attached to scaffolds. An exemplary set of moieties is described below.

In an exemplary embodiment of the invention, a subset of the above moieties is used. Use is made of the rotational flexibility of hydrogen bond donors and/or receivers. Although such flexibility will generally reduce chemical bonding probability, the mass of a hydrogen atom used in a hydrogen bond moiety is sufficiently low that the reduction in probability may

not materially affect the results of the measurement method, at least for some gauges and assays.

Alternatively or additionally, rotational flexibility is allowed for aromatic rings. Although aromatic rings have a high mass, the large bond area of the ring compensates for the reduction in bond strength caused by allowing rotational flexibility of the ring.

Alternatively or additionally, some polar bonds may be represented by a single moiety, such as OH, which can act as both a hydrogen bond donor and as an acceptor.

Optionally, for example if chemical information can be done without, more general moieties are used and a smaller number of triangles in a library is spanning.

5.5 OVERLAP OF MEASURES IN A SET

In an exemplary embodiment of the invention, the triangle space as a whole is spanned by providing a plurality of triangles, each with sufficient freedom in its parameters (e.g., bond length, chemical affinity), so that each triangular arrangement of binding points can be expected to bind to one of the triangles to a measurable degree. Optionally, the coverage of each triangle in the triangle space overlaps with the coverage of other triangles, to ensure that no parts of the space are left uncovered.

As will be explained in greater detail below, in an exemplary embodiment of the invention, a gauge library is designed such that each possible triangular arrangement of binding points appears in (or fits within the parameters of) more than one gauge. In some cases, exactly congruent triangles cannot be provided, instead, triangles that are roughly congruent are provided (e.g., similar moieties, side lengths). These congruent triangles may have the same coverage in triangle space or not. For example, assuming same moieties, two triangles with the following side lengths are provided: (3, 4, 5) and (3.1, 3.9, 5.2) (measurements in angstrom. These triangles may, for example, cover the part of triangle space from (2, 3, 4) to (4, 5, 6).

In some embodiments of the invention, at least some of the triangle space is spanned by a set of triangles with overlapping coverage. For example, for the same part of triangle space, the provided triangles are (2, 3, 4.5) and (2.5, 3.5, 5.3), which have overlapping, but different coverage.

While overlapping is useful for various reasons, for example, as described below, it does increase the size of the library. When overlapping is provided, the reconstruction method used optionally takes the overlapping into account.

6. RECONSTRUCTION

After process 300 (Fig. 3) is repeated for as many gauges as desired, the measured affinities of gauges 400 to target 100 are optionally used to reconstruct a model of the spatial distribution of interaction areas 102. An exemplary method is described below.

In an exemplary (theoretical) mapping process for a particular target molecule, which uses a 75,000 gauge library, it is expected that about 400 of the gauges will bind to the target. Due to repetition of triangles in the library and/or due to the overlap in coverage of non-congruent triangles in the exemplary library, the number of real triangles defined by the target area and bound to by gauges is expected to be smaller. In one (theoretical) example, the number of "real" triangles that are defined by the target area and bound to by gauges is 100 different triangles.

Taking for example a 10-point pharmacophore, such a pharmacophore may include, for example, 10*9*8/6 triangles, which is 120 triangles. In some embodiments of the invention, not all of these triangles are identified, for example, due to high similarity between triangles (below distinguishing ability) or due to lack of binding (e.g., due to steric clashes). The 10 point structure can, of course be reconstructed with fewer than 100% of the triangles, especially of the missing triangles are missing randomly. For example, 50% of the triangles may be sufficient.

However, the actual situation is more forgiving. A typical pharmacophore may include 20 points, of which, typically only between 8 and 10 need to be identified in order to provide good binding. Thus, any substructure of the pharmacophore that includes 8-10 correct points can serve as a good starting point for drug generation. Fewer identified points can also be useful, for example as described below.

Although various methods may be used to reconstruct the layout, in an exemplary embodiment of the invention a two step method is used. First, the "real" triangles are estimated from the results of the assay, optionally using a clustering algorithm. Then, a suitable layout using the triangles is found, optionally using a scoring based search algorithm or a clustering algorithm. In other implementations, a single step or multiple step method may be used.

6.1 TRIANGLE EXTRACTION

In an exemplary embodiment of the invention, this step of the process has two parts, however, in other implementations, this step has a single part or more than two parts. One part is determining which triangle measures matched. This part may be less than trivial, for example, due to the fact that each gauge includes multiple triangles. However, the repetition of

triangles between gauges may assist in differentiation. Another, optional, part of the process is determining the real distances involved, rather than those defined by a measure. For example, a real distance between two moieties may be 4.3 angstrom, while binding triangle measures have distances of 4 and 5 angstrom. In some embodiments of the invention, it is desirable to

5   estimate the real distance, 4.3 angstrom, from the binding results. Optionally, this is provided by the overlap in coverage of the different triangle measures.

In an exemplary embodiment of the invention, the two parts of the process are provided in a single compound process, for example using clustering. Alternatively a two step method may be used. Optionally, an iterative method is used with an estimate of which measures

10   bound being used to estimate real distances and the real distances being used to improve the earlier estimate of which measures bound.

Fig. 5 is a flowchart of a method 500 of determining which triangles did bind to a target, in accordance with an exemplary embodiment of the invention.

At 502, a space is defined for each type of triangle (defined by the moieties of the

15   triangle). Each such space has three dimensions, each one representing a length of a side of the triangle.

At 504, a notation is made in a space at a location {x,y,z} if a gauge including that type of triangle with sides of lengths {x,y,z} was shown to bind to the target. It should be noted that for two different scaffolds, exactly matching triangles may be difficult to generate. Instead, the

20   triangles may be nearly matching, for example having slightly different lengths of sides.

In an exemplary embodiment of the invention, the assay results are used as a binary input, there is either a bond or not. Alternatively, for example if conformal changes are observed or there is a measure of activity and/or bonding, the bond strength may be represented by a continuous or multi-step amplitude, using a hit notation.

25   In an exemplary embodiment of the invention, if a single gauge includes multiple triangles, a hit is marked in each one of the relevant spaces. Alternatively or additionally, if a single triangle can match two different type triangles, for example due to overlap between moiety affinity, it is also marked in multiple spaces. Optionally, the amplitude of the marking is normalized to the number of spaces that are marked by the gauge. Alternatively or

30   additionally, a different amplitude is provided in each space, responsive to an a priori probability of bonding.

At 506, the hits notations are replaced by a spatial spread function. In an exemplary embodiment of the invention, the spread function represents the probability of that triangle

forming a bond at different distances represented by the spread. Alternatively or additionally, the spreading is between spaces, for example, if two moieties overlap in their affinities.

Alternatively, the hit indication is provided originally as a spreading function.

In an exemplary embodiment of the invention, the spreading is a defined as

5
$$f = e^{-\frac{\Delta x^2}{\sigma x^2}}$$

where Δx is the difference between the lengths of the sides and σx is a value representing the difficulty in bending the molecule so that it can perform the bond. In an exemplary embodiment of the invention, σx is a function of x, for example $\sigma x = a\sqrt{x}$. In an exemplary application, parameter "a" is 1.414. Possibly, the spread function is non-uniform in space, for
10   example, to reflect non-uniform characteristics of the bond. Optionally, at least some of the spreading functions are derived empirically, by binding gauges having controlled distances between bonds, with targets having known models. Alternatively or additionally, such empirical testing is used for other purposes, for example, to determine flexibility in bond length, multiple chemical affinity of moieties and/or symmetry of the spreading function.
15   Optionally, targets are classified according to their flexibility as well. Optionally, in an iterative process, once a model is estimated, a flexibility of the target is estimated and/or decided, for example form a table, and used to correct the spreading function used.

The spread hits are then combined, for example by addition, and peaks are found in the result (508). In an exemplary embodiment of the invention, peaks are selected based on their
20   shape. Alternatively or additionally, peaks are selected based on their amplitude passing a threshold. This threshold can represent, for example, the number of triangles that need to bind, to indicate a possible match. The threshold may be the same for all spaces or it may be different. Optionally, the threshold and/or decision making method is selected based on the clustering statistics, for example from a table of previous empirical results. Alternatively or
25   additionally, the threshold is selected so that a minimum number of matches be found. Optionally, if there is a large number of sub-threshold matches, a different gauge set is used for the binding process. It is noted that in some embodiments of the invention, for any given triplet of binding points there are generally about 12 triangles, or more, that can be expected to bind. For example, both a shorter side and a longer side are expected to bond to a pair of binding
30   locations having an intermediate distance between them. In addition, each triangle type can appear multiple times, for example, three times in the set. In some sets, each (or some) triangle

point in the triangle space is covered by 24 triangles - 8 triangle designs that have longer and shorter sides in various combinations, times 3, if each triangle is provided three times. Additional overlap may be provided by ambiguous moieties.

Optionally, by analyzing correlation between spaces and gauges, some four-point geometrical matching (or higher) may be found as well.

6.2 LAYOUT CONFIGURATION RECONSTRUCTION

Fig. 6A is a flowchart of a method 600 of determining a spatial layout of binding locations from the results of the method of Fig. 5, in accordance with an exemplary embodiment of the invention. In an exemplary embodiment of the invention, the method comprises constructing all the configurations (e.g., three dimensional shapes) that can be constructed from the identified triangles and ranking the configurations using a scoring method, ultimately selecting the configuration with a highest score.

At 602, all the possible configurations that can be constructed from the triangles found in Fig. 5, are constructed. Alternatively to building computer models of all the possible configurations, in an exemplary embodiment of the invention, the configurations are generated ad hoc. For example, in conjunction with the scoring method described below, a configuration may be constructed, or its construction advanced, only if it is likely to have a useful score. For example, once a configuration solution has a score below the highest found so far, that lower solution is ignored.

In an exemplary embodiment of the invention, the construction method is by building up a structure piece by piece. For example, a triangle is added to an existing configuration only if has a side length and/or moieties that match a side length with a pair of moieties on the structure. A threshold of size difference may be defined for allowing the matching of two sides. Alternatively or additionally, a threshold of matching between moieties may be defined. Optionally, the moieties are required to match at the ends of the matching side, or to have an overlapping chemical behavior. Such thresholds may depend on the length and/or types of moieties and/or other properties of the gauges and/or the target. It is noted that a first gauge may bind to a particular binding location using a different binding method from a second gauge, as long as the binding location supports both binding methods.

In an exemplary embodiment of the invention, the construction of a configuration is by sequentially selecting a triangle from the list of available (bond) triangles, until all the triangles are used at least once. Used triangles may remain in the list for repeated use. Alternatively, the

configuration may be built up using modules, each of which is constructed from sub-modules, and, ultimately, triangles.

At 604, a score is calculated for each configuration. Such a score is optionally a heuristic value indicating the reasonableness of the assay results being derived from the target

5   having the configuration. Various scoring methods may be used. In an exemplary embodiment of the invention, the scoring method is based on the particular linking together of triangles in the configuration and/or on the probability of the triangles themselves being correct in the first place.

In an exemplary embodiment of the invention, the score is a product of scores for each

10   shared triangle side. In an exemplary embodiment of the invention, the score for a triangle side that is shared between two triangles is an estimated probability of the two sides of the two triangles binding to a same pair of binding locations. In an exemplary embodiment of the invention, the score is the product of the above spreading function, for the x, y and z axes. Alternatively or additionally, other, simpler scores, may be used, for example, based only on

15   the difference in sizes of the sides.

In an exemplary embodiment of the invention, the score does not depend on the lack of a triangle. For example, if a generated configuration includes a three point configuration for which no suitable gauge matched, it is not assumed that the configuration is incorrect, nor is the score reduced. Alternatively, the score may be reduced responsive to the existence of

20   triangles that are found in a configuration and not found on any matching gauge, for example, based on their count.

Alternatively or additionally, some configurations may be ruled out based on heuristics, for example rules that describe what the layout typically looks like. Alternatively or additionally, prior information is used to rule out some configurations, for example, a partial

25   model or knowledge of a molecule that binds well to the target.

At 606, the structure with the highest score is selected as the map layout of the binding locations for the target. As noted above, 602-606 may be carried out as an iterative search and construction method, for example with structures being built ad hoc as the search progresses and indicates a certain structure has a score above a threshold (and so will its dependents).

30   Many suitable search methods are known in the art, for example, in the art of graph search and in the art of searching game trees (e.g., for chess playing programs).

6.3 RECONSTRUCTION VARIATIONS

In an exemplary embodiment of the invention, a target may have several active areas. In an exemplary embodiment of the invention, the reconstruction is allowed to recreate a disjoint configuration structure, with each disjoint part representing a map of one target area.

5   Optionally, such a reconstruction may be required even for a single active area, if enough triangles (e.g. gauge moieties) that interconnect the disjoint parts failed to bind (for various reasons) and/or were not available in the gauge set used, so that a continuous structure cannot be reconstructed from the triangles that did match.

Optionally, the above reconstruction allows a triangle to appear only once in a

10   reconstructed configuration. Even if a triangle actually appears twice (or more) in the real configuration, the redundancy of similar triangles will generally still enable the structure to be reconstructed. Alternatively or additionally, a triangle is allowed to appear more than once, however, this may affect the score, for example, reducing it. Alternatively, an iterative experimental approach, as described below, is used, to block part of the target (e.g., with a

15   suitable antibody or small molecule drug) and see if the triangle still matches.

Optionally, user intervention is allowed, for example, for viewing the final structure or several candidate structures. For example, if a determination cannot be made, a human may be requested to select among options, force certain matches and/or configuration parts and/or to remove certain possibilities from consideration, based on, for example human experience and

20   judgment and/or additional information about the target of various types.

It should be noted that one possibly output of the clustering and/or shape reconstruction methods is an input to an interactive process and/or to further drug development. For example, the application of the above methods can show where more exact data is lacking for forming a complete result and/or where there are ambiguities between possible solutions.

25   It should be noted that the resulting structure may have a mirror (e.g., symmetry) ambiguity, due to the sole use of triangles. Optionally, this ambiguity is solved by using at least one 4- or higher- point measure, optionally constructed or selected to bind in only one of the possibilities. Alternatively or additionally, the effect of steric clashes is used to distinguish between the two possibilities. Alternatively or additionally, prior information is used to

30   distinguish between them.

6.4 ALTERNATIVE RECONSTRUCTION METHOD

Fig. 6B is a flowchart 620 of an alternative reconstruction method, using clustering for shape reconstruction, in accordance with an exemplary embodiment of the invention.

At 622, a triangle is selected from the set of found triangles, that were found to bind in the assay and clustering of Fig. 5. This triangle is used as a base for constructing a structure.

At 624, a pair of triangles is selected from the remaining found triangles, such that the two triangles share a side with each other and each triangle also shares a side with a part of the structure (e.g., which two sides of the structure may or may not be sides of a same triangle, depending, for example on the implementation). When the triangle pair is added to the structure the structure grows by one point in space.

624 is repeated (626) until no triangle pairs can be added. This completes one potential structure.

Often, there are several possible choices to make at 624, for example, for selecting the triangle pair and/or for deciding where to add them. At 628, a tree of possible structures is performed, by repeating 624 and 626 for each possible choice of triangle pairs and their location. This process may be done, a priori, for example, by spawning multiple threads each time multiple triangle pairs are available for selection and/or each time such pairs may be attached at different locations.

At 630, 622-628 are repeated by selecting all possible triangles as bases, in turn (or in parallel). Alternatively, other methods of generating all the possible structures from the triangles may be used. Optionally, a pruning method is used, for example, if a structure is clearly unsuitable or unable to utilize a significant percentage of the triangles (e.g., 30%, 50%, 70% or any smaller, intermediate or greater value), the structure is dropped. Generally, the greater the number of triangles allowed to be ignored, the easier it will be to provide a structure (e.g., even under noisy conditions) . However, the structure will be less constrained by the assay results and may be less dependable.

At 632, all substructures found in the generated potential structures. Optionally, only some of the substructures are found, for example, only the largest or only those above a certain size. In an exemplary embodiment of the invention, the method applied is a maximum likelihood algorithm for finding a most likely structure.

At 634, these substructures are clustered, with each point representing a structure in which the substructure is found. In an exemplary embodiment of the invention, the clustering space is defined per triangle type (e.g., type of moieties on the triangle) and the space is spanned by the sides of the triangles. Thus, for example, a 10 point sub-structure of a 20 point structure is marked in a space that includes the same number of moiety types as the sub-structure, with a location in that space determined by the three Cartesian locations of each of

the points (e.g., 30 dimensions for a 10 point sub-structure). Various orientations are optionally dealt with by selecting a certain triangle to be a base triangle having an orientation. Alternatively or additionally, the space is marked with structures in a rotationally symmetric manner (or thus analyzed) so that the results from different orientations may be compared. An exemplary algorithm is described in R. Nussinov, H.J. Wolfson, "Efficient Detection of Three Dimensional Structural Motifs in Biological Macromolecules by Computer Vision Techniques", PNAS, volume 88, pp. 10495-10499, December 1991, the disclosure of which is incorporated herein by reference.

At 636, a best substructure is selected. It is assumed that if a substructure is common enough and large enough it is both correct and useful. In an exemplary embodiment of the invention, a thresholding is applied to select only those substructures with structures and clusters over a minimum size. Other selection methods may be used as well, for example scoring, for example based on accumulated score of matching up pairs of triangles (this matching up may be thresholded during constructions, for example using a preset threshold).

Alternatively, other methods of finding a large common substructure are used.

It should be noted that while the clustering method may generate a structure that does not use all the triangles and is not complete, a complete map of the pharmacophore is not essential for many embodiments of the invention, for example for lead generation and finding.

7. ANALYSIS

7.1 OVERVIEW

The above process of measuring and reconstructing a target area can be used to provide a wide range of information. The quality of the information and its type can be of varying kinds. Following are exemplary types of parameters which may be used to classify such information:

(a) Completeness. The information may be complete or partial, for example, a complete target area model or a model of only part of an area.

(b) Factual or statistical. An example of factual information is an exact model. An example of statistical information is a set of relative probabilities for a set of possible models.

(c) Independence. Information may be independent of other information, for example, being an exact model or it may be dependent, for example a parameteric model whose exact value depends on additional information. In addition, information derived using the above methods may be used as partial information for a different process.

(d) Substantiation. The information may be supported by other information or it may stand on its own or even be in conflict with other information.

(e) Positiveness. The information may be positive, in that it indicates what exists if is desirable, or negative, in that it can be used primarily to knock out certain possibilities.

5   While the information garnered may be about the binding locations, in some case, the information is regarding the geometry of the target at non binding locations as well. As will be described below, for example, a geometrical structure can also affect the usefulness of a drug lead.

In some embodiments of the invention the analysis is used to acquire information about 10   the gauges themselves, for example, their relative binding affinity, and/or their chemical behavior (e.g., pH dependencies). Such information may be general or it may be for groups of targets, for example, different for different families of proteins and the same within a family.

As can be appreciated, such a widely varying range of information is amenable to many methods of analysis, some of which are described below and to many applications, some of 15   which are also described below. In particular, some exemplary analysis methods are directed to garnering further information about the target area and for error detection and analysis and some exemplary applications are integrated as part of a drug discovery process.

In some case, the results of the analysis are integrated into the reconstruction as geometrical and/or chemical information. Alternatively or additionally, the information is 20   associated with the reconstruction and/or the target, for example, in a manner similar to that used for drug leads. This manner generally depends on the type of database used for storing information.

7.2 RECONSTRUCTION VERIFICATION

In an exemplary embodiment of the invention, the error size and/or type of the layout is 25   determined. In one example, the reconstructed layout is analyzed to generate theoretical binding values for the gauge set used. Differences between these theoretical binding values and actual binding values may be used to indicate parts of the layout which are not exact and/or to indicate a degree of inaccuracy of the layout and/or the reconstruction process as a whole.

Alternatively or additionally, physical verification is applied, for example, by applying 30   an additional testing method and/or assay library to select between alternatives or for verification.

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7.3 BINDING STRENGTH

In an exemplary embodiment of the invention, the generated layout is analyzed to estimate the relative binding strength of binding points in the target area. In an exemplary embodiment of the invention, the reconstructed layout is modeled and theoretical binding values for the gauge set are calculated. Variation in the actual binding values may be partly caused by a reduced or increased affinity of target area. Such estimation is generally statistical in nature since there are many variables that affect binding probability. However, it is expected that if a bond length and type are known and the exact positioning of the gauge in the target area can be determined (e.g., and its energetic consequences), than at least a statistical analysis of binding strength may be provided. Optionally, a baseline is provided by analyzing molecules with known behaviors, or by comparing the binding of different, but similar gauge-triangles.

7.4 INTER-BOND INTERACTIONS

In an exemplary embodiment of the invention, the analysis is used to determine an interaction between the binding of different binding points. For example, such an analysis can compare the contribution of a binding point to the binding of a certain gauge, as compared to what is expected (e.g., based on energy and other calculations) and/or as compared to the apparent contribution of that binding point to the binding of a different gauge. This may indicate, for example, the effect of the bonding to one interaction location on the affinity of a neighboring interaction location. Optionally such interactions are estimated and/or modeled using a model of electronic charge distribution in the target.

7.5 GEOMETRIC ANALYSIS

For some purposes, and to some degree of accuracy, the determined layout can be considered to be a cast of the target area. In an exemplary embodiment of the invention, the geometry of the target area is analyzed. Additional information may be provided by determining which gauges did not bind or bound with a lower affinity (which, if the binding geometry was similar is assumed, in some embodiments of the invention, to be due to steric clashes). This may assist in further defining the geometry of the target area. It should be noted that some steric clashes can be predicted from the geometry of the layout. Any failed binding which has no other apparent reason and should have matched the determined geometry, may be assumed to result from a projection of matter that does not define a noticeable binding point. This is described in more detail below.

In an exemplary embodiment of the invention, the geometric analysis is used to determine a size of entry hole into area 104 (e.g., where arrow 400 is shown in Fig. 4B). A small hole and/or certain moieties at the hole entrance may rule out the possibility of certain drug sizes and/or types. Alternatively or additionally, the geometrical analysis is used for

5   classifying the target, for example, based on the size of substrate that it might work on. In an exemplary embodiment of the invention, geometrical analysis (e.g., for substrate determination) is supported by chemical analysis of the moieties in target area 104. Determination of the geometry may also be useful in deciding what marking methods of small molecules and/or gauges may work (e.g., not to use large florescent markers, if the entry hole

10   is small).

It should be appreciated that in some cases it may be easier to reconstruct the geometry of a target area, rather than its chemical binding pattern or vice versa.

7.6 DETERMINATION OF STERIC CLASHES

In an exemplary embodiment of the invention, steric clashes are detected in the analysis

15   process and/or used to provide additional geometric and/or chemical information about the target. In an exemplary embodiment of the invention, steric clashes during the binding process are determined by comparing the affinities of different gauges with same triangles. This comparison optionally takes into account one or more of entry hole size, chemical behavior of the gauge, degree of matching to the binding geometry and/or other binding locations. Steric

20   clashes are, for example, caused when the proximity or potential overlap of the gauge and the target molecule reduce the binding affinity.

As the shape of the gauges is known and, in some embodiments of the invention relatively rigid, steric clashes may be expected to result from the non-participating moieties of the gauge and/or the scaffold itself.

25   In an exemplary embodiment of the invention, the steric clashes are used to generate a map of locations near the target that interfere with gauge atoms, thus possibly indicating occupied (e.g., by atoms, electric fields) parts of the target, which do not, apparently cause a binding interaction with any gauge, to a noticeable degree.

In an exemplary embodiment of the invention, the map is used to provide further

30   information about the shape of the active area in target 100. Alternatively or additionally, the map is used for assisting in drug development, for example, by filtering out potential drugs that would have the same steric clashes. Optionally, some level of filtering can be achieved simply

by matching the drug geometry to the geometry of gauges that should have, but did not, bind well.

Geometrical and/or chemical affinity analysis may also be used to determine a shape of the natural substrate of the target, for example, if it is not clearly known and/or to determine

5   which part of the substrate is engaged by area 104.

7.7 IDENTIFICATION OF CONTROL AREAS

In an exemplary embodiment of the invention, the binding results and/or reconstruction are analyzed to detect one or more control area of the target. Generally, control areas do not bind to the "main" substrate of the target, instead binding to a separate hormone or other

10   modifier molecule. This secondary binding typically affects the binding behavior of the target area.

In an exemplary embodiment of the invention, control areas are identified by their size and by their being disjoint from a main target area layout reconstruction. Alternatively or additionally, control areas are identified by testing bindings with pairs of gauges (or in the

15   presence of various molecules, optionally selected a-priori or after the detection of the presence of control areas) to detect intra-gauge binding dependence. Alternatively or additionally, control areas are identified from the shape of the reconstructed layout. Alternatively or additionally, the presence of control areas is detected by there being left-over gauge bindings that are not needed and/or do not fit in the reconstruction.

20   In an exemplary embodiment of the invention, depending on whether binding to a control area is desirable or undesirable, the differential identification of control areas may be used for screening potential drug leads.

7.8 OTHER MAP ANALYSIS

The map or model of the target may be analyzed to yield other information, in

25   accordance with exemplary embodiments of the invention. For example, as noted above, the distance of a binding point from a control area or active area can affect the type of drug developed. For example, a drug that binds in the control area may have an enhancing effect on the target, for example that of an agonist. A molecule that binds near the control area or active area, or inside the active area, may cause the target to be less sensitive to signals and/or

30   incapable of acting, e.g., an antagonistic effect. Thus, in an exemplary embodiment of the invention, the location of the binding area on the target is used to assist in determining what

sort of therapeutic effect to expect from a developed drug. For example, a binding area near a target area may indicate a drug whose tail blocks access to the target area.

In another example, binding areas that are outside the target area, can be used to enhance a drug design. A drug may be constructed (or discovered) to include parts that bind in the target area and parts that bind outside the target area. The combination of binding areas provides a binding strength greater than that provided individually by each area, while the part of the molecule bound in the target area can provide the desired therapeutic effect. Alternatively or additionally, a molecule that binds to two separate areas may cause a conformal change or prevent such a change in the target molecule.

8. USE IN DRUG DISCOVERY PROCESSES

8.1 OVERVIEW

Drug discovery is a very long and expensive process whereby drugs for curing diseases are found. The process starts with identifying a target to be affected by the drug, finding potential drugs that affect the target and then determining which, if any of the potential drugs is safe and dependable. Often, no suitable drug is found and one of the drug candidates is modified in various ways in an attempt to make it more suitable. One cause of difficulty of the drug discovery process is the difficulty in knowing what molecule will affect the target. As will be described below, in some embodiments of the invention, the methods of the invention are used to at least partly reduce this difficulty. Another cause for difficulty is the many unexpected side effects of potential drugs which render them unsuitable and/or unpredictable. Again, as described below, some methods of the invention may be used to at least partly reduce this difficulty.

Typically, drug discovery methods try to answer two questions. One, is there/what is a drug molecule that binds strongly and affects a target molecule. Two, how to ensure that these drug molecules have the proper ADMET profile (ADMET stands for Absorption Distribution Metabolism Excretion Toxicity) which translates into success in clinical trials. In an exemplary embodiment of the invention, the method, materials and/or apparatus described herein are used to select, design and/or aim towards potential drug molecules that have chemical characteristics that are known or believed to improve the ADMET profile. Lipinski rules are an example. It should be appreciated that by knowing which parts of the molecule are relevant to binding and which are not (as provided, for example by comparing a molecule to a model of the target), one can more easily modify (or plan in advance) potential drug lead compounds to bind tightly and/or meet any well defined qualities.

In general, the above methods and especially the various models of the target can be useful in selecting molecules or research methods that conform to the map and rejecting those that do not. Other uses of the above measurement process are also described below, for example using an additional step of mapping to check a theory. As can be expected, different

5   methods (existing and new) of drug discovery may be affected differently by the use of exemplary embodiments of the invention.

It should be appreciated that various embodiments of the invention may be implemented in an automatic manner. However, due to the great cost considerations, in some embodiments of the invention, the application is semi-automatic, for example, using the

10   methods to change the discovery process, for example, by adding a filtering step or a candidate generation step, while still allowing for the use of human judgment, for example, deciding if certain generalized and vague criteria are met. In some case, the entire process is controlled using a human intelligence, with various ones of the steps, for example, mapping and/or rejecting leads are performed manually. Changing thresholds and redoing a step is an example

15   of a decision which may be reserved for a human, for example.

8.2 DRUG GENERATION

One relatively new type of drug discovery is actually drug generation, a new molecule is designed to have a desired function. In an exemplary embodiment of the invention, the above chemical and/or geometrical map of the target are used to assist this process. For

20   example synthesis may be assisted by showing what shape an active part of the drug must have (or limit the range of possible shapes).

In an exemplary embodiment of the invention, drug synthesis comprises taking gauges from the library and modifying them, for example replacing moieties, so that they better match the target. In some cases, the replacement moieties have the same affinity but a different

25   binding strength, for example, selecting NH2 or OH for a Hydrogen bond donor, and choosing an optimal size for a for hydrophobic moiety. It should be appreciated that an strength based classification of moieties may also used in the library construction, for example, providing multiple strengths of Hydrogen donors or multiple sizes or hydrophobic moieties. One possible use is to achieve a better uniformity of binding strength between moieties. Another is to

30   provide a library with higher accuracy.

In an exemplary embodiment of the invention, scaffolds and/or molecule parts for use in drug synthesis are constructed as a result of target mapping processes. For example, by analyzing target geometries, a set of scaffolds that spans (with attached moieties) most of the

target spaces may be found. The specific scaffolds may be, for example, constructed from sub-scaffolds or be selected from libraries of chemicals, for example using a process similar to that described below for finding gauges in libraries. Sets of moieties or moiety clusters may be selected, for example based on a statistical analysis of how moieties are clustered together in a

5   family of targets or in a general list of targets. Optionally, the statistics are collected over the mapping of many targets. Optionally, the targets are selected to be exemplary for expected future targets. It is expected of course, that in some cases a perfect drug will not be generated using such synthesis methods, but the synthesized drug may be a good starting point for drug enhancement.

10   ## 8.3 LEAD GENERATION

       Often simpler than drug synthesis is lead generation, in which a lead, which is not expected to be a suitable drug, is generated and then enhanced and modified using processes known in the art. In an exemplary embodiment of the invention, the map is used to describe a potential molecule, for synthesis as a drug lead. In an exemplary embodiment of the invention,

15   the map is used as a set of constraints and a search is made to find a molecule meeting the constraints. Additional constraints can be, for example, known synthesis methods, a base molecule form being used as a starting point. An exemplary software which may be used is LUDI sold by MSI (USA). The LUDI system operates by attaching basic chemical components together in order to obtain a required pharmacophore-match or other molecule.

20   The potential molecule may then be synthesized and developed into a drug, as is well known in the art.

       In an alternative method, a potential drug molecule may be constructed by linking together molecules of the gauge library or other molecules having suitable moieties or structure, so that the resulting molecule has a higher affinity than a single gauge. This

25   molecule may then be optimized, for example by removing unnecessary moieties and/or adding moieties to provide various desired properties. Optionally, the gauges are attached using a scaffold, rather than directly to each other. Optionally, by analyzing what gauges link (e.g., using clustering), it is possible to achieve a better estimate of a desired size and/or chemical properties of the fragments to be linked. For example, the selection of two gauges to

30   be linked together may be based on actual binding of additional (or other gauges), for example, 2, 4, 5, 6 or more gauges. For each such set of gauges that bind, a best gauge or other molecule is selected for the linking. Alternatively or additionally, higher specificity gauges are used to determine which of the several possible triangle measures of a gauge actually bound. Such

higher specificity gauges may be generated, for example, by removing moieties from existing gauges (or generating such gauges using any method known in the art). Such higher specificity gauges may also be used for other embodiments of the invention, for example, to improve clustering statistics. Generally, however, due to the relative large number of possible such

5   gauges, they are used when there is a way to limit the range of possible triangles. Alternatively, the large number of more specific gauges, for example, gauges with 1, 2, 3 or 4 triangles are created for use as a library or as part of a library of gauges.

In an exemplary embodiment of the invention, knowledge of the structure of the target is used to correctly locate the linker and/or chose a suitable linker that does not suffer steric

10   clashes with the target.

In an exemplary embodiment of the invention, the gauges are selected for linking without actually constructing a model. Instead, the actually binding gauges are selected and linked together. Alternatively, the model is used to decide which gauges to link and how to link them. Such a model may also be used in other lead-linking schemes, for example, as

15   described in the background, to guide the choice of which fragments to link, what length of link to provide, where to attach and/or at what orientation to attach. Optionally, the lead is constructed in steps from the gauges, and each step is tested to see if it meets its expected behavior.

Alternatively or additionally, instead of using a model as provided herein, a different

20   type of model is used, for example a model of the target bound to a gauge, for example generated using X-ray Crystallography and/or NMR. This model, for example, generated once for each of a plurality of gauges may be used to decide what linking distance and type to provide when creating a lead from gauges. Alternatively or additionally, a new molecule may be designed and constructed to have binding points at some or all of the locations shown by the

25   crystallography model to bind, for example, for two, three or more gauges. In general, this type of method assumes that once the configuration of the bound target-gauge pair is known, an exact model may be unnecessary, since actual conformance information is available. Alternatively or additional, as noted herein, a measurement may be made of the bond target.

8.4 LEAD DESCRIPTION

30   In an exemplary embodiment of the invention, the map is used to describe one or more profiles of molecules which would be expected to have an effect on the target. In an exemplary embodiment of the invention, the profiles generated take into account one or more of:

(a) geometry of interaction location layout;

(b) affinity of interaction locations;

(c) size of entrance into the active area(s);

(d) identification of potential control area(s);

(e) synthesizability; and

(f) expandability, e.g., that additional moieties can be attached.

Typically, a molecule requires at least five or six bonds to form a strong enough docking in the target, so as to affect the a target at nano-Molar concentrations. The exact number may depend, for example, on the affinity of the interaction locations. A single target will generally provide a large number of possible profiles. These profiles may be matched against libraries, for example, using methods known in the art.

In an exemplary embodiment of the invention, the profiles are generated using a format that is matched for a particular search software and/or library data structure. In an exemplary embodiment of the invention, searching by pharmacophore is provided, for example as known in ISIS base from MDL (when searching 3D databases).

8.5 LEAD SEARCH

In an exemplary embodiment of the invention, the map is used to search through a library of known molecules, for a possible match. Possibly, the map is used in place of analytical models of the target, in known virtual scanning techniques. In an exemplary embodiment of the invention, the library is pre-processed so that molecules in the library are described in terms of the moieties and geometries of the layout model and/or the gauges used in measuring the target. Alternatively or additionally, an existing library is pre-processed to yield a gauge-compatible description of its contents, for example, each molecule being defined as a parametric model based on measurement gauges. It should be noted that this description may not be a one-to-one mapping, for example, a same molecule may be described using two different sets of moieties, as there is some overlap between moieties chemical behavior.

In an exemplary embodiment of the invention, potential leads are identified based on them including or being able to include a large number of moieties at the required positions, as indicated by the map. In one example, a search is made for 3 point or higher (e.g., 4, 5, 6, 7 or more) matches. In another example, each molecule in a library is tested for the number of moieties it includes in the required positions and for the availability of attachment points to attach missing moieties. In an exemplary embodiment of the invention, the missing moieties are added one by one until a suitable drug lead (e.g., strong enough binding) is created.

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An exemplary search is performed by ISIS base, by MDL.

One possible type of search comprises going over all available 3D structures in which to search, breaking them down into sets and/or subsets of pharmacophore points and looking for a fit within a tolerance range defined in a query.

8.6 *LEAD REJECTION*

In an exemplary embodiment of the invention, the results of the above methods are used in rejecting leads that otherwise appear suitable. In one example, a lead (or family of leads) is rejected if the above models imply a lack of binding and/or steric clashes. In another example, an assumption is made that if a lead is suitable, a gauge corresponding to a triangle (or other number) of moieties on the lead is expected to bind to the target. If no such gauge is found or an analysis of the data implies that the probability of a triangular binding of the three moieties in a gauge is unlikely to have happened, the lead is rejected, or subjected to additional scrutiny. Alternatively or additionally, a matching of a certain gauge may also indicate the lead is unsuitable.

In one example, workers in the field can use the information provided to determine if a certain lead is likely to be capable of being optimized (reasonably). For example, one expects that by directly adding or removing specific moieties (e.g., what is often considered to be a main type of small changes in a molecule) affinity can be significantly improved (often at least 3-4 orders of magnitude are required). By knowing what the changes should be or could be (e.g., where additional points need to be added, which information may be provided by some embodiments of the invention) one can see if one specific lead can undergo the required changes, e.g. has putative attachment points in the right positions. Specific gauges (e.g., that bound) will indicate what the required changes could be.

These methods may also be used to reject certain lead modifications provided during lead enhancement processes.

It should be noted that some lead rejection methods do not require all possible gauges and/or triangle measures to be available. Rather, even a partial library is useful, for example for rejecting certain leads. In one example, a partially-spanning library is used generating a partial map (e.g., part of space, disjoint and/or not all binding points), which can be used to reject some leads and/or indicate potential suitability of others and for search. Further, even the binding or failure of binding of a single gauge may indicate suitability or lack of suitability of a lead. Generally, due to the uncertainty involved in all chemical processes at this time, decisions are not made on the basis of a single binding assay.

8.7 TARGETED MAPPING

In some embodiments of the invention, gauge binding is assayed during the discovery process. In one example, the binding is used to test a theory or an assumption regarding the leads. For example, if a certain lead is expected to be suitable, at least one of several particular gauges may be expected to bind. Leads may be ranked, for example, based on how well such targeted binding is. Alternatively or additionally, a part of the layout may be remapped as a result of the discovery process. For example, the discovery process may indicate conflicting evidence of the layout structure. In another example, a higher resolution mapping of part of the layout may be required, for example, to more exactly determine the distance between two moieties. In some cases, instead of assaying with a full set of gauges, gauges are selected based on them being most likely to bind (or not) to the particular desired parts of the layout. For example, if the distance between two points on the layout needs to be determined, gauges that are less likely to bind at other points of the layout are selected. In another example, the moieties used are more specific, for example, having a more limited repertoire of chemical behavior and/or have a greater directionality. This may require using a different scaffold. Possibly the gauges used for such remapping have fewer triangles per gauges, for example between one and three, to reduce unexpected binding probability. Alternatively or additionally, gauges are selected so that steric clashes prevent binding in undesired locations. In some cases, these gauges are not in the basic mapping library used for initially determining the layout. In some cases, the required gauges are synthesized ad hoc, rather than selected from an existing library.

8.8 TARGET SUITABILITY TESTING

In an exemplary embodiment of the invention, the map is used to determine the suitability of a target to be a target for a drug. A suitability value may be, for example binary or it may be graded (discrete or continuous). In some embodiments of the invention, a suitability value is not a scalar, for example, being a vector, with each element of the vector indicating a different aspect of suitability. A similar structure may be used to indicate suitability of leads and potential drugs.

One example of the use of target suitability testing is where there are multiple potential targets. For example, in some diseases, there is a possibility of selecting between a plurality of target proteins, or selecting different parts in the chain of protein synthesis (e.g., DNA transcription, protein-chain creation, protein folding, protein post-processing and protein deployment). Some of these potential targets may be unsuitable.

In an exemplary embodiment of the invention, the map can be analyzed to detect such suitability, for example, by rejecting targets with an active area that is too large (for some types of treatment). The size of the target area can be detected from the layout geometry. Alternatively or additionally, a target may be deemed unsuitable due to its having a too

5   generally active (non-specific) target area, which can be determined, for example, by analyzing the specificity of the determined target layout. Alternatively or additionally, a target may be deemed unsuitable, because its active area that has very weak affinities (e.g., a large drug molecule with many binding points may be required). Alternatively or additionally, a target may be deemed unsuitable due to its similarity to a housekeeping protein. This similarity may

10   be determined by comparing the layouts of the target with those of known housekeeping proteins. Similarity to any human protein may assist in determining potential side effects ahead of time. In lead grading, a lead may be evaluated based on a probability of its interfering with a housekeeping protein, which is optionally determined by checking the binding of a lead to model layouts of housekeeping proteins.

15   In an exemplary embodiment of the invention, a database of layouts of housekeeping proteins is provided. such a database may be provided using methods known in the art. Alternatively or additionally, at least part of the database is provided by systematically mapping housekeeping proteins. Alternatively or additionally, at least part of the database is provided by generating "worst case" target area geometries or a range of possible geometries

20   for the active areas, based a knowledge of the structure of substrates that are acted on by the protein. Such a worst case target area may also be used as prior information to assist in deciding which of several reconstructions is correct.

8.9 TARGET PARTITIONING

In an exemplary embodiment of the invention, the map is used to identify parts of the

25   target as being potential "exact" targets, and on which the drug discovery method can be focused. Although the target, as a whole, is what is being affected by the drug, it can be affected in many ways, for example, different drugs may block different parts of an active area. Alternatively or additionally, some drugs may cause conformal changes. Alternatively or additionally, some drugs may interact with control areas on the target. Alternatively or

30   additionally, some drugs may be agonistic, while some antagonistic. Alternatively or additionally, some binding areas may be useful for staging (e.g., as a base for attaching molecules closer to a target area), rather than direct activity. Binding areas may be classified based on the type of effect that may be expected from a molecule binding to those areas. This

classification may be, for example, manual. Alternatively or additionally, automatic classification may be provided, for example, based on target template structures (e.g., which indicated for a certain class of protein what each area of the protein might do).

Optionally, potential control areas that can change the target, are identified. Possibly, such control areas are identified based on a binding in a binding assay. Optionally, a model of the target is used to assess whether binding at the potential control location can cause conformal changes, for example, based on the proximity of interaction locations on different, adjacent parts of the protein.

In an exemplary embodiment of the invention, the active areas are segmented into different "exact targets" based on the sub-areas that have a potential for drug interaction, for example, based on their geometry. Alternatively or additionally, segmentation is based on selecting such sub-areas that are not common to similar sub-areas of housekeeping proteins (e.g., segmentation into special and common binding areas).

8.10 DRUG AND LEAD ANALYSIS AND ENHANCEMENT

In an exemplary embodiment of the invention, the above layout is used for analyzing existing drugs or drug leads, for example, to assist in improving or reengineering the drug or in screening.

In an exemplary embodiment of the invention, the layout is used to determine which of a plurality of target areas on a target are interacting with the drug or which target from a plurality of possible targets are interacting with a given drug. This methodology may be used, for example, to analyze the effect of drugs whose operation method is not clear.

In another example, the drug is analyzed to determine which part of the drug binds to the target. This can serve as a basis of a process for modifying the drug, in which the binding parts of a drug are retained and other parts of the drug are modified. Alternatively or additionally, when modifying the drug, care is taken not to distort the active part of the drug so that it does not bind, or distort the drug as a whole so that steric clashes are caused.

It should be noted that a single drug may interact with two different targets in a desirable manner, each target interacting with different, possibly overlapping, parts of the drug. Such activity of a drug is optionally determined by comparing the drug structure to that of the targets.

In some cases, the exact spatial and chemical properties of the drug (or a protein substrate) are not known. However, by determining the layout of targets which bind to the

drug, the spatial and chemical layout of the active part of the drug (or substrate) may be estimated.

In another example, the layout is used to determine the pharmaceutical activity of synthesis byproducts. When a drug is produced using a particular process, various byproducts are produced as well, some with a beneficial activity and some with a non-beneficial activity. In an exemplary embodiment of the invention, the structure of such byproducts is compared to target areas of the target and of housekeeping proteins in an attempt to estimate what side effects they might cause. A process for drug manufacture is optionally selected or rejected based on a thus-estimated activity of the byproducts, given that the type and amount of byproducts produced by a particular process can be determined. Alternatively or additionally, such comparison may be used to assist in improving a production method and/or in deciding which synthesis parameters to use. This testing may also be used for regulatory purposes, for example to approve or disapprove generic drugs.

8.11 DRUG SELECTION

In many cases, there may be multiple drugs which can treat an illness. Knowledge of which target (and housekeeping proteins and/or other human proteins) is affected by a drug and how it interacts can be useful in selecting between alternative treatments, in preventing side effects, preventing or controlling drug-interactions and/or in selecting treatments for diseases that no exact drug has been selected for, for example exotic tropical diseases and some viral diseases.

In an exemplary embodiment of the invention, the layout of a target is used to select which of a plurality of available drugs or drug leads appears to be most suitable for interacting with a the target. In the case of drugs, this may allow selecting alternative treatment protocols. Also, in some cases, knowledge of the interaction method will assist in selecting those times and/or associated protocols and/or drug combinations at which the drug is most effective and/or has minimal side effects.

Alternatively or additionally, drugs may be designed to interact with multiple targets. For example, a lead that interacts with multiple targets (e.g., of a same or different disease or syndrome) or target area portions may be awarded a higher scoring for further processing that other leads.

A possibly related use is the finding of a new use for an old drug and/or assisting in determining how to modify an old drug for a new use. For example, when searching for leads that match a template, a search may also be made through databases of drugs, to see which

drug has a structure that is prophesied by the modeling process to provide good binding. Existing drugs, in general, have the other properties (ADMET).

8.12 DRUG ENHANCEMENT

As noted above, knowledge of the interaction method and/or problems of interaction
5   with a target area, can assist in modifying a lead to become a drug. Alternatively or additionally, such knowledge may be put to use in enhancing an existing drug and/or modifying a drug to interact with a target related to an existing target. By comparing the layouts of the two targets, for example, possibly useful changes in a drug may be determined. Alternatively or additionally, the layout of the target area may be used to assess problems with
10   the binding of the drug to the target (e.g., too strongly or too weakly) and/or determine the effect of modification of the drug on such binding behavior. In an exemplary embodiment of the invention, the potential drug when bound is assessed against the model, to determine if a moiety exists that can be theoretically added, which will bind to another point in a binding area.

15   Alternatively or additionally, drug enhancement comprises enhancing a drug to match more than one target, or a variety of target mutations, for example including one moiety to bind for one mutation and one moiety to bind for another mutation, for example, in HIV some proteins have two main varieties and countless sub-varieties. This enhancement may interfere with other properties of the drug, but the tradeoff may be considered useful.

20   Alternatively or additionally, a drug may be designed to bind to a subset of binding points that is common to a plurality of targets or mutations, for example, models of the plurality of targets are analyzed to determine shared binding points. The various drug discovery methods are then optionally applied assuming that only these binding points exist. Real assaying of a potential drug may be carried out on the multiple targets to ensure that the
25   various modifications of the drug did not make it fail to bind to one of the targets. Alternatively or additionally, when a modification is made, it is determined whether the modified drug will bind to the common binding locations and/or have steric clashes. It should be noted that there might be other reasons to discover a drug that binds only to a subset of the possible binding points, for example, if a mutation is expected in one of the binding points
30   and/or to allow the drug to work even if an interfering molecule is bound to one of the binding points.

8.13 DRUG FAILURE ANALYSIS AND REENGINEERING

Often, a drug will come out to market and then fail. The method described herein may be useful in determining a reason for the failure and then possibly assisting in rescuing the drug. In an exemplary embodiment of the invention, the layout of the target of the drug and/or other proteins that the drug is believed to have interacted with (e.g., based on the type of side effects), are generated. The drug is then compared to the targets to determine failures in binding to the correct target and/or undesirable binding to non-targets. It should be appreciated that while such comparison may be theoretically possible using other means, it is believed that prior to the availability of target mapping, such large scale molding of active areas of targets was not practical, due to time and cost limitations.

In an alternative embodiment of the invention, it is noted that a drug may be suitable for only part of the public, for example, due to individual differences. In an exemplary embodiment of the invention, the genes that express inadvertent targets and/or targets are used to reconstruct models or samples of the targets and then map the active areas of the models. The results may show that an individual has a sensitivity to the drug and/or that a different individual is resistant to the effects of the drug. Alternatively or additionally, the testing may be done against pathogen strains, to determine differential sensitivity to drugs. In some cases, the genetic differences are linked to already known markers, for example sensitivity to sulfates is linked to a G6PD deficiency for sulfates, so that the classification of people as being compatible with the drug may be simple. Alternatively, a genetic test may be applied prior to selecting which drug to use on a person.

8.14 ADDITIONAL DRUG DISCOVERY RELATED ANALYSIS

Additional analysis methods may also enhance a drug discovery process. For example, many drugs have side effects due to their interaction with housekeeping proteins or proteins that cause feeling of malaise if interfered with. Examples include GI proteins and liver proteins. Some drug targets are known to be similar to such proteins. In an exemplary embodiment of the invention, models are generated for such potential side-effect generators. Any potential drug lead is rejected (or scores lower) if it is shown to bind to one of these prohibited models. Alternatively or additionally, drugs that have a known side effect are analyzed to determine which protein they bind to and this protein and/or the particular binding locations are used for defining a prohibition of binding of a potential drug.

In another example of an analysis, potential drug molecules are analyzed to see if they bind as a substrate to certain enzymes. Such binding may indicate a speed of incapacitation of

a drug or its excretion. Alternatively or additionally, such binding may be useful for identifying pro-drugs, that are activated by their interaction with certain enzymes, such as liver enzymes. In this case, a drug may include two sets of active areas, one for activation of the drug and one for binding of the drug to its target. Optionally, biding to a protease (or other manipulating

5   protein) is ensured by adding binding moieties or gauges to a drug molecule at suitable locations.

In another example, a set of target molecules that are all known to be affected by a same protein or molecule are analyzed to determine of they have common binding geometries to which the molecule bonds. This may help, for example, in fine tuning the molecule to bind

10   more selectively, for example, by adding a moiety which will interfere with other target molecules and/or assist in binding to a particular target molecule.

8.15 STREAMLINE DISCOVERY PROCESS

As can be appreciated a discovery process typically includes going through various dead ends. In an exemplary embodiment of the invention, mapping of the targets is used to

15   select parts of the discovery process that are likely to fail and prevent them from being attempted. Some examples (some of which are described elsewhere in this application) include, dropping targets that do not seem suitable for improvement, identifying targets likely to have side effects and weeding out libraries. In an exemplary embodiment of the invention, weeding out existing libraries is performed by removing from a library leads that have an

20   expected low probability of binding and/or appear redundant to other molecules. For example, a molecule that is very flexible is less likely to bind. The probability of binding may be estimated, for example using energetic considerations based on the molecule's degrees of freedom.

8.16 UTILITY GENERATION

25   While many proteins and molecules are catalogued, many of them do not have a known utility. Determining an exact utility for a protein or a molecule may require a very large expenditure. In an exemplary embodiment of the invention, potential utilities for molecules and for proteins may be generated on a large scale in the following manner. A molecule may have a utility as a gauge or it may have a utility as a lead or drug. In an exemplary embodiment

30   of the invention, existing target area layouts, for example, 10, 50, 100, 1000 or any smaller, greater or intermediate number are matched to the molecule to see if binding is likely. It is

expected that many molecules will turn out to have a potential utility. In general, more matching is more work, but increases probability of success.

In a similar manner, mapping proteins provides an indication of its active area shape, potential substrates and/or potential drugs which might affect it. In an exemplary embodiment of the invention, a utility is found for a protein by determining its substrate. Optionally, the protein active area layout is compared to structures of known substrates and proteins.

In this manner, a library and individual drugs and proteins may be said to have an expected utility. For example, the protein may be for one of the following protein families GPCR's, Proteases, Kinases, Ion Channels messenger proteins or any type of peptide or other macro-molecule found in a living organism.

9. EXEMPLARY DISCOVERY APPLICATIONS

9.1 OVERVIEW

In this section existing discovery methods will be described, as well as possible modifications that take into account the methods described herein.

While many approaches to drug discovery are known, the following two main approaches generally encompass the existing methods.

9.2 SCREENING BASED DRUG DESIGN

This discovery method works by screening a target against a large number of molecules and then attempting to enhance any matches to produce a drug. The process is as follows:

(a)   Provide a general library of compounds for screening, equally relevant to all target proteins. Typical sizes of such libraries grow constantly at roughly one order-of-magnitude (factor of 10) per decade. Current typical sizes are 1-10 million. The libraries are often proprietary and maintained by each corporation independently.

(b)   Screen the corporate library against the chosen target. Look for compounds exhibiting at least weak activity (significant activity at concentrations typically 1-100 μM) of the type required with relation to the target.

(c)   If no hit is found, the process ends here. Apparently, this is often the case, possibly in above 70% of the cases. If hits are found, an optimization stage is initiated, in which the final outcome is expected to be a compound with strong activity (at concentrations typically nM) against the target. This is done in one or a combination of the following two methods:

1.   In case there is only one hit or all hits are variations of one molecular theme, a large number of analogues of the hit are synthesized. This group of compounds is sometimes known

as a "focused library". These are also screened against the target protein. The purpose here is to define a direction for increasing the activity of the original hit by identifying chemical moieties and positions on the original hit that increase activity. This process is known as developing a QSAR (Quantitative Structure Activity Relationship).

5   2.   If a number of chemical groups have been identified as hits, a computational process of identifying possible pharmacophores (molecular substructures directly involved in binding of the hits to the target) is executed. These may indicate not only possible directions for optimization, but also their feasibility for a given molecular starting point (both from a physical point of view and from a synthesis point of view).

10   (d).   Drug like qualities are generally a byproduct of this process. Molecules in the initial screening library are often chosen to possess drug-like qualities. During the optimization process, only partial information is available so that simultaneously satisfying drug-like requirements and increased activity are seldom under direct control. Final drug-candidates that may result from this process closely resemble hit compounds in the initial screening library.

15   (e)   Testing. The drug-candidates are tested, for example in live animal models and then in humans, to determine there efficacy. Many drug candidates fail at this point and lacking any basis for modification, fail completely.

In an exemplary embodiment of the invention, the above described inventive methods may be used to improve the above drug discovery process, for example one or more of:

20   (a)   Hit rate. As stated above, in most cases, no hits are found for a new target. By generating a mapping of the target, the leads used for screening can be better selected. Even leads with very weak affinity may be selected for further improvement, due to the combined indication of very weak activity and matching a map. Alternatively or additionally, the method of designing a gauge library is applied to a molecule library, to reduce duplication and to assist

25   in ensuring coverage of binding space. This may be done, for example, by analyzing the library to identify gauges in triangle space and/or uneven distribution leads in this space. In addition, excessive overlapping may be determined. Alternatively or additionally, the library may be analyzed to determine molecules that are unlikely to ever bind, for example, due to them having excess flexibility and no known binding partners. Alternatively or additionally, if the

30   screening is in stages, molecules may be selected for each stage based on them having less overlap with each other.

Alternatively or additionally, some binding results may be ignored, for example, molecule with high flexibility may add too much noise (binding to many molecules in many ways) and therefore be ignored, at least in a first stage of processing.

Alternatively or additionally, the gauges that bind can themselves be used as leads (and many of such bindings are expected). Often the gauge library is small compared to the corporate library and can be added to it with a relatively small penalty. In an exemplary embodiment of the invention, results from the "old" library will serve as initial starting points for optimization (as before) but optimization will be directed by information gained from screening using gauges. Possibly, a gauge library binding assay is performed on a target with an interacting lead. This type of assay can be used to determine if the lead (or molecule from a library) is interacting with the active area or not (e.g., based on whether and the extent that it affects the binding of the gauge library). This assay may be compared to an assay performed with other binding leads and/or with no bound leads at all. The effect of lead chemistry may be determined by checking the assay in the presence of one or more chemically similar but non-interacting leads.

(b) Process directing. If the target is mapped and a lead starting point is known, there are still many ways of enhancing the lead to produce a drug. In an exemplary embodiment of the invention, knowledge of the target geometry and/or chemical behavior is used to assist in directing the modification process, replacing physical experiments with virtual ones and/or assisting in culling out (probably) useless leads. In addition, it is noted that various combinatorial generation of lead modifications can be simplified by selecting only those lead modifications that are meaningful (or are most meaningful) in view of the target layout and/or based on the three-dimensional structure of the leads (e.g., by checking which triangles are exhibited by which lead and by which lead modification). Optionally, a mismatch between the results predicted by the determined layout and actual binding activity of the leads may be useful in correcting the layout, better understanding the chemistry of the lead and/or predicting other leads that might show promise.

(c) Drug recovery. Even if a drug fails the final testing stages, in an exemplary embodiment of the invention, the above methods may be used to determine the reasons for the failure and/or provide guidance in reengineering the drug.

9.3 ALTERNATIVE SCREENING BASED DRUG DESIGN

Chemical genomics or chemogenomics have lately become very popular. They are based on the idea that instead of first finding a target first and then finding a compound for it,

the opposite process is applied: first screen compounds against whole cell assays looking for the phenotypic result (e.g., selective death of cancer cells). Then, once an active compound is found, the target is sought. One possible advantage of this approach is working in parallel on multiple targets, many of which may not even be known. However, existing screening libraries

5   cannot guarantee finding hits. In an exemplary embodiment of the invention, a gauge library as described herein is used and is expected to have a plurality of gauges that interact with the cells. While the interactions may be weak, a non-trivial number of such interactions may be expected.

9.4 STRUCTURE-BASED DRUG DESIGN

10   This method assumes that accurate modeling software for simulating molecular processes is used. The process is as follows:

(a)   Obtain an accurate and detailed three-dimensional structure of the target protein. Usually done via X-ray crystallography or NMR analysis (both experimental). Computational approaches also exist, but are generally not accurate.

15   (b)   Identify the active site in the protein structure (not always straightforward for new, unfamiliar targets).

(c)   Identify relevant binding points in the active site, also known as pharmacophore points. These are points where weak (non-covalent) binding can occur. A potential Ligand must satisfy a number (usually 6 or more) of these points simultaneously in order to achieve nM

20   affinity.

(d)   Design molecules that "fit" the active site, both geometrically and in terms of satisfying enough pharmacophore points. Both this stage and the previous are done using "docking" or molecular-mechanics type simulation software.

In an exemplary embodiment of the invention, the herein described inventive methods

25   may be used to improve the above drug discovery process, for example one or more of:

(a)   Linked structure. 3D structures of proteins are apparently, in many cases, of little use in and of themselves. Much experience has shown that it is difficult to design strong binders based on this (e.g., geometrical) information alone. In an exemplary embodiment of the invention, it is noted that useful information is present in 3D structures of the target with

30   bound ligands. While such ligands are not known initially, in an exemplary embodiment of the invention, gauges that bind to the target are used in place of such ligands, with the expectation that a significant number of such binding gauges will be found. In an exemplary embodiment of the invention, the gauge binding process is applied and then the target is modeled (e.g.,

using NMR or X-ray crystallography), possibly several times, with different gauges linked. The shape of the target area with the linked gauges is expected to be useful for designing strong binders using methods known in the art. Possibly, the known methods may be modified, for example, to combine the results of different configurations caused by different binding

5   locations of different gauges. Optionally, the provision of multiple binding gauges (e.g., 5, 10, 25, 50, 100 or any smaller, intermediate or larger number) will assist in determining the binding mode(s) of the target, possibly enhancing the understanding by providing partial binding modes as well. In general, the provision of more gauges, means more work, but may enhance the accuracy of the analysis.

10   In an exemplary embodiment of the invention, the linked structure results from a plurality of gauges are combined, for example by super position with the target as a reference. This superposition may yield a total model of the binding area of a target and/or fully bound configuration, rather than a partial one might be provided by each gauge.

(b)   Comparison. In an exemplary embodiment of the invention, the shape of the

15   active area determined by the simulation model is compared to the shape of the area as determined by the mapping process. Differences between the two may assist in correcting the mapping/reconstruction method or it correcting the simulation model. Optionally, the simulation model is used to select between alternative reconstruction and/or to assist in fine-tuning a reconstruction, for example, by assisting in calculating more exact distances and/or

20   indicating which possible moieties could be taking part in the binding.

(c)   Identification of binding points. In general, modeling software is not accurate enough to predict binding points in a protein target. Also active areas may be difficult to identify. This is especially the case for novel targets. In an exemplary embodiment of the invention, the above methods circumvent one or both of these problems by identifying

25   potential binding points/modes experimentally, e.g., using a standard assay library of gauges. Then these active areas are analyzed in greater depth using docking software, for example to predict the affinity of new compounds to a specific target.

9.5 MODULAR ASSEMBLY OF LIGANDS

This method, which is apparently used by Sunesis inc., works by constructing leads

30   from parts that show affinity. The process is as follows:

(a)   Synthesize a finite library of elementary molecular fragments that include a "linker port" (i.e. a site on the molecule at which linking can be easily implemented). These are

typically small molecules previously identified as pharmacologically "interesting", and which are amenable to including the standard "linker port".

(b)   Screen the elementary fragments against the target protein, looking for extremely (~1mM) low affinity. This step is typically problematic.

5   (c)   Link groups of two or more fragments via their "linker port" components in order to achieve increased affinity. The distance between two fragments, i.e. the length of the linking chain, may be varied and optimized.

In an exemplary embodiment of the invention, the herein described inventive methods may be used to improve the above drug discovery process, for example one or more of:

10   (a)   The elementary fragments are currently not designed in the art using any logic that may be viewed as exhaustive, i.e. typical diversity metrics are used (as in standard screening libraries) but these do not yield a finite list. Consequently, hits are seldom found (for general targets), even less than for general screening libraries, probably due to very low affinity expected, which poses many technical problems (e.g. solubility). In an exemplary embodiment

15   of the invention, the set of fragments is selected based on spanning the space. For example, fragments may be pairs (or triplets) of moieties, having distances and moiety types selected to span the possibility space.

(b) Geometry, i.e. the proper distance and orientation between two weakly binding moieties, is totally absent from the initial screening results in the art. In the linking stage, only

20   very limited geometry variation may be tried (i.e. the length of the linker). In an exemplary embodiment of the invention, the binding of a gauge library is used to provide geometrical hints (or a complete model) which assist in deciding how to put together fragments, which fragments to put together and what distances to set between the fragments. This may also assist in determining what type of linker to use when linking fragments. This may also be used for

25   synthesizing a new molecule that includes the binding parts of the binding gauges, spaced apart by a suitable structure (e.g., a variation on a known drug).

10. EXEMPLARY NON-DISCOVERY USES

The above measurement methods may also be applied to uses other than drug discovery. A different gauge set may be required for some uses.

30   In one exemplary embodiment of the invention, the measurement methods are used to assess toxicity, for example, to identify housekeeping proteins that may have adverse interactions with a certain drug or potential toxin. This may be useful in determining toxicity of industrial or household chemicals.

In another exemplary embodiment of the invention, the measurement methods are used to predict antibody affinity to a material and/or cell, for example by identifying binding sites on an antibody and/or a material.

In another exemplary embodiment of the invention, the measurement methods are used to map the outside of an organism, for example, a virus, rickettsia bodies, worm, protozoa, fungus, ameba or a bacteria. This may be useful in the development of vaccines. For example, a vaccine is often more effective if it is made from a protein whose shape does not change. By determining which parts of the binding areas on the outside of a pathogen do not change, such determination may assist in selecting a particular protein from the pathogen for vaccination use and/or to assist in assessing the chances of creating a useful vaccine. In order to prevent auto-immune responses, the active areas of existing vaccine material may be mapped, to see if the pattern resembles that of bodily proteins to too great an extent. It should be noted that this matching may be dependent on an individual's genetic material.

Alternatively to absolute measurements, in some embodiments of the invention, the above methods are used for determining relative measurements, for example, for measuring conformal changes in a protein, under different conditions. A same (or different - e.g., to match new expected measurements) binding assay may be applied to the protein under different conditions. Possibly, more flexible gauges and/or less stable gauges are used for this application.

In another exemplary embodiment of the invention, the above measurement method is used to find new agricultural chemicals, such as insecticides and herbicides that are target-specific by affecting proteins known to be crucial only for some types of pests or weeds. Alternatively or additionally, artificial hormones are developed to match targets in plant cells.

11. USING PRIOR INFORMATION

The above process has been described, in some examples, as a blind process, which assumes a neutral starting point of substantially no knowledge about the target. In some cases, there exists prior knowledge about the target, gleaned from various sources and/or by previous measurements of the target. Such prior information may be used in many ways. Following are some examples.

In an exemplary embodiment of the invention, the prior information is sufficient to propose several alternatives. A binding assay with the gauge library, with or without reconstruction may provide enough information for selecting between the alternatives, for example between alternative models of which part of a lead interacts with a target or selecting

between two target area layout reconstructions. Optionally, to this end, the gauge set can be reduced to only those gauges that will distinguish and/or that are needed by either one of the models.

In another example, crystallography, NMR, IR spectrum and/or chemical properties of the target are used in the above reconstruction process, for example, to resolve ambiguities and/or to overcome lack of data. In one example, these methods show how one or more gauges actually bind in the target. In another example, these methods or other prior knowledge are used to force a certain structure to be reconstructed, rather than following the above described score based reconstruction. For example, forcing the structure to include a certain sub-shape (e.g., a tetrahedral portion) that would not otherwise be reconstructed from the assay data.

In another example, if part of the target is known, it can be reacted with a substrate that blocks out that known part, so that the measurement will only apply to the unknown portion. Alternatively, the statistics of interaction in the known portion may be used to assist in associating binding statistics with structure in the unknown portion. For example, a computer model or an analogue target may be used to provide an estimate of which gauges bind and at what strength, to the known portion. In the assay results analysis, gauges that bind to the known area are ignored, not used in the assay and/or their binding strength reduced during the analysis. Optionally, a gauge is not removed from consideration if removing it will leave no triangles of a certain size and/or moieties for binding to the unknown area. Alternatively, the library as a whole is used, for example, as noted above that simultaneous screening using 100,000 assays at a time, is a current technology.

In another example, when an iterative measurement method is used, prior information may provide insight into desirable starting points.

Optionally, the prior information is used as an input for modifying the binding process, for example by varying the binding environment.

In another example, the prior information is used to set the environmental conditions used during measurements, for example, using information from previous assay attempts with a similar protein to indicate what environmental conditions are likely to provide bindings and/or at least not interfere.

In an exemplary embodiment of the invention, prior information is used for the design of specific scaffolds, moieties and/or gauges to better measure a particular target. The molecules may be, for example, designed ad hoc, and/or a sub-library constructed by selecting previously known molecules. In an exemplary embodiment of the invention, a scaffold is

selected for such a sub-library due to a small (e.g., 0.5 A) difference in a side of a triangle due to the change in scaffold. In a regular mapping process, such a difference may not be important, but in high-resolution mapping, for some targets (e.g., where binding is weak) it may be important. Similarly, a set of gauges may be provided to cover a certain range of sizes

5   and/or chemical behaviors at a finer resolution.

12. ITERATIVE MEASUREMENT

In some ways similar to the use of prior information, iterative measurement allows information form a previous measurement step to be used, for example, to better tune a current step or to reject certain possibilities.

10   In some embodiments of the invention, instead of a one step measurement process, for example as described in some of the embodiments above, an iterative measurement method is used. In one example of this method, a lower resolution reconstruction is generated. Then additional assaying is performed, using a same or different gauge library and a higher resolution reconstruction is provided. The earlier reconstruction may be used, for example, as a

15   starting point for the reconstruction process and/or to assist in selecting which gauges to use in the additional assaying. In an exemplary embodiment of the invention, such an iterative method is used, for example, when the cost and/or time to perform a single complete assay are large.

In an exemplary embodiment of the invention, an iterative measurement uses more

20   flexible gauges (explained below) in a first set of measurement than in a second set of measurements. Alternatively or additionally, a different subset of gauges is used for the different sets of measurement.

The difference between the stages may be in correctness of the reconstruction, for example, which interaction locations lie where. Alternatively or additionally, the difference

25   may be in accuracy, for example, in the distance between two binding locations or the bond angle of an interaction location. In an exemplary embodiment of the invention, the above assumptions of range coverage, for example, for hydrophobic bond sizes and for directional bonds are made stricter in later reconstruction iterations, for example, providing 15 directional bonds. However, not all the measurements may need to be redone. Instead, only those gauges

30   that bond to interaction locations that are expected to change in the model, are used. Various search methods known in the art may be used to assist in providing and/or determining convergence of the assay and reconstruction process, for example, hill-climbing.

13. GAUGES, PHYSICAL PROPERTIES

13.1 OVERVIEW

Various uses of gauges are described above, some of which may use a complete gauge library (e.g., completely spanning and having sufficient resolution) and some which may, alternatively or additionally, use a partial library. One or more of several issues are optionally considered in the design of such libraries. Exemplary such issues and considerations that may optionally be used when designing and/or selecting gauges, gauge designs and/or gauges sets are described below. It is noted that some of the issues relate to the properties of the individual gauges and some to the properties of the gauges as a set. The design (and/or selection) of a complete set of gauges may address multiple issues and various tradeoffs, for example as shown in the exemplary gauge set described below. These issues are explored below. In general, it should be noted that even some of the gauges in a gauge set are not useful, this does not generally detract from the usefulness of the gauge set as a whole.

Fig. 4A showed an exemplary gauge 400. A typical gauge set includes a large plurality of gauges. Possibly, all the gauges share a basic common design, as will be described below, however this is not essential. In addition, there can be many gauges, gauge designs and gauge sets that are useful for measurement.

In an exemplary embodiment of the invention, a significant portion of a gauge set is based on permutations of a small number of basic molecules, called scaffolds. In this design method, a scaffold includes a plurality of attachment points and each gauge is created by selecting a scaffold and mounting various moieties at the attachment points. One potential benefit of this approach is that fewer different chemical processes are required for synthesizing a library. Another potential benefit is that the generated library has more predictable chemical behavior, reflected, for example in the environments used for assaying. Another potential benefit is that a more predictable and/or controlled set of distances between moieties may be achieved. Another potential benefit is simplicity is designing a spanning library. Another potential benefit is that it is easier to ensure spanning in a library or library portion. Another potential benefit is using this type of permutations (possibly with scaffolds novel to the library) supports generation of missing or desired measures, ad-hoc. In one case, for example, new gauges with particular distances are generated by modifying an existing scaffold. It should be noted that not all these potential advantages are expected in every embodiment of the invention.

It should be appreciated that for a given library, parts may be based on scaffolds, while other parts are generated using other means, for example, selection form an existing molecular library and/or constructed using various molecular construction, design and synthesis methods known in the art for attempting to custom create molecules with certain properties. Further, the

5 entire library can be non-scaffold based. It should also be appreciated that not all scaffold-based libraries provide all, some or even any of the above potential benefits.

13.2 SCAFFOLD

In Fig. 4A, gauge 400 is shown to include a scaffold 402, to which four moieties are attached, at four of possibly more potential attachment points. In an exemplary embodiment of

10 the invention, gauges 400 are selected to span a range of distances between moieties. In an exemplary embodiment of the invention, by varying the locations of connection of moieties among available attachment points, different inter-moiety distances are fixed for a single scaffold. A greater range of possible values is optionally achieved by providing a range of possible scaffolds. It should be noted however, that no scaffold is required, per se. Rather, it is

15 expected that at least for some embodiments of the invention, it may be more cost effective to create a library combinatoricly using scaffolds. This is exemplified in Fig. 4B, where the gauge is shown as a triangle defined by its moieties and the distance between them, without any reference to the scaffolding.

However, in an exemplary embodiment of the invention, a scaffold is provided on

20 which multiple different gauges are constructed. A plurality of different or same moieties may be selectively attached to different locations on the scaffold, using relatively standardized methods of combinatorial-chemistry, thus creating a range of gauges, possibly having generally known chemical properties (e.g., solvency, vapor pressure, stability).

In some embodiments of the invention, the scaffold(s) is selected so that it does not

25 extend to or out of the triangle shape(s) defined by the moieties. Alternatively or in some cases, the scaffold and/or some of the moieties do interfere with the binding, and may cause steric clashes. By providing a range of scaffolds, steric clashes may be avoided for some gauges and/or the causes of the steric clashes may be determined.

In some embodiments of the invention, the scaffold geometry and/or chemistry is

30 meaningful.

Optionally, the participation of the scaffold in the provision of binding triangles is ignored in the design of the gauge set. Alternatively, the scaffold chemical activity is noted during the design of the set, for example, for providing one or more moieties. Optionally, the

effect of the scaffold on providing binding, repelling and/or interfering bonds, is considered during reconstruction or analysis. Alternatively or additionally, the geometry of the scaffold is taken into account during analysis, e.g., to determine causes for steric clashes.

Alternatively or additionally, triangle binding analysis ignores any binding triangles that are probably not exposed to the target (e.g., based on gauge geometry).

13.3 VOLUMETRIC GEOMETRY OF GAUGES

Triangles, as a rule, define a plane, which may or may not be the plane of the scaffold (if any). In an exemplary embodiment of the invention, when gauges are selected for inclusion in a library they are selected so that their attached moieties lie in a plane or in some other desirable conformity. A planar arrangement has a potential advantage of preventing multi-stable (e.g., conformal changing) molecules from being included, which is not desirable in some embodiments of the invention, as they may confuse the analysis and/or reduce the binding probabilities. Possibly, a set of gauges is provided, to cover a range of possible non-planar orientations. In some embodiments this is more desirable than selecting a molecule that exhibits conformal changes. Molecules with conformal changes may be excluded using other methods as well, for example, by analyzing each potential gauge. Alternatively or additionally, the gauges are selected so that the dimensions of the gauge or of particular triangles in it do not change, even if other parts of the gauge exhibit conformal changes. Optionally, a certain triangle in a gauge may be neutralized by making it energetically unlikely to bind, for example, by ensuring that that triangle exhibits conformal changes or adding flexibility to the bonds of one or more of its moieties. It should be noted however, that such exact modification of a gauge may not be possible, for example, due to the small size of a gauge or its possible effect on other parts of the gauges and/or other triangles.

13.4 FLEXIBILITY

The flexibility of a gauge can adversely affect one or both of the amount of information provided by the gauges matching and the affinity of the gauge to the target. While it is true that flexible molecules are more likely to find an arrangement of points to bind to, increased flexibility may, at least in some cases, reduce the overall probability of binding of a molecule, for entropic reasons. In addition, the binding of a flexible molecule provides less precise information than the binding of a rigid molecule.

Thus, although a greater number of interaction location layouts can be matched using a flexible gauge, in an exemplary embodiment of the invention, at least some relatively rigid

gauges are selected for the gauge library, so that the measurements using these gauges are more precise. Optionally, substantially all gauges in a gauge set are substantially rigid. In an exemplary embodiment of the invention, the gauges are translationally rigid, in that the distance between moieties does not change much. Alternatively or additionally, the gauges are rotationally rigid, in that the relative orientation of the moieties does not change. Optionally, flexibility extends to chemical specificity of the moieties, for example, by selecting moieties that are either more or less specific. For example, one can chose moieties that have only one function (i.e., for hydrophobic chose tert-butil or a non-aromatic ring (e.g. cyclohexane) or for hydrogen bonds avoid using a hydroxyl (OH) (which is both a donor and acceptor), or vice versa.

In an exemplary embodiment of the invention, however, a small degree of flexibility is provided, for example to ensure overlap between gauges. In one example, the degree of flexibility is sufficient so that a pair of moieties in the target can be matched by multiple pairs of moieties in the gauges, with different distances between them. In an exemplary embodiment of the invention, the gauges are designed such that each distance between moieties in the target can be matched both by a gauge that has a slightly longer distance and by a gauge that has a slightly shorter distance. The degree of flexibility may be defined so that a relatively low amount of energy is required to bend or stretch the gauge so that it can match the moiety layout in the target. The relevant energy levels may depend, for example, on the assay sensitivity, on the gauge concentration and/or the assaying environment.

Optionally, at least a small number of the gauges are flexible, for example to compensate for gauges that are not available. For example, as noted herein, rotational flexibility may be allowed for hydrogen bond participants and/or aromatic rings. Alternatively or additionally, flexible gauges are used to assist in providing coarse level information which may be later fine-tuned using rigid gauges. Optionally, the reduced amount of information (e.g., by lack of binding and/or less precision) is compensated for by the redundancy of the gauges and triangle measures in the gauges.

It should be noted that particular method of determining which triangle bound, described above, provides a significantly greater weight to rigid triangles. It should be noted that in a single gauge, triangles may have different rigidities.

In an exemplary embodiment of the invention, the Catalyst software from Accelrys (formerly MSI) is used to assess the rigidity of a gauge.

In an exemplary embodiment of the invention, at least 20%, 40%, 60%, 80% or any smaller, intermediate or larger percentage of the gauges are rigid. In general, if more rigid gauges are used, they are easier to analyze using the methods described herein. However, such gauges may not be available and/or it may be desirable for various reasons to use non-rigid molecules, for example, if such molecules are similar to drugs or have other properties believed to make them suitable for screening.

In an exemplary embodiment of the invention, a substantially rigid molecule (or bond) is defined as a molecule which has a single entropic configuration and, in which, except for hydrogen atoms, no bond changes by more than 1Å using less than 20kCal/Mole. Alternative embodiments of the invention may allow less rigidity, for example allow greater movement, such as 0.8 Å, 1.5 Å, 2 Å or any greater, smaller or intermediate value, at 10 kCal/Mole, 15 kCal/Mole, 30 kCal/Mole, 40 kCal/Mole or any smaller, intermediate or greater application of energy. It should be appreciated that absolutely rigid molecules are generally not possible. Instead, the term "substantially rigid" is used in the claims. As the molecules become less rigid, they may bind with more difficulty and be less specific in the meaning of their binding. However, less rigid molecules may be easier to obtain and/or use to ensure coverage, for example.

Typically, rigid molecules are those for which all single bonds are either part of a ring or attach "end" atoms i.e. at one of their ends (e.g., single atoms or simple moieties such as NH_2, for which rotation is uninteresting in some cases). Once the ring grows too much, for example beyond 5 or 6 atoms in some cases, the ring becomes flexible. Larger rings may also be rigid, for example, if there are never more than 2 adjacent single bonds whose atoms participate only in single bonds (i.e. if any of the atoms in the ring are themselves attached by a double bond to an atom that is not a member of the ring, this also may rigidify that segment of the ring). A single covalent bond is rotationally free, unless it is part of a ring.

13.5 GAUGE LENGTHS

In an exemplary embodiment of the invention, the gauge sides lengths (i.e., the distances between the center of mass of the moieties) are selected to cover a range of expected distances between interaction locations and/or dimensions of small molecule drugs. Alternatively, for example, for non-small molecule drugs, a different range may be selected than for small molecule drugs. In an exemplary embodiment of the invention, the selected range is between 2 Å and 12 Å. In another example, the range is to under 10 Å, or under 8 Å. Alternatively or additionally, the range is from above 3 Å or above 4 Å. In some cases, an

"outer length" or an "inner length" may be useful, which are defined from the outside or inside of the moieties taking part in a triangle.

In an exemplary embodiment of the invention, the sampling is selected to uniformly sample an energy cost required for a molecule to accommodate the sampling resolution. For example, if a first triangle side is x Å and a second triangle side is y Å, the range of distances covered by the first side should require a same amount of energy to modify the molecule to fit the range, as the range of distances covered by the second side. Generally, this means that as the molecule is larger, the binding range, for a same amount of energy, increases. Optionally, the allowed amount of energy is a parameter of the assaying process, the target and/or the gauges used, for example, to allow a detectable binding by the gauges.

In an exemplary embodiment of the invention, the range is covered by intermediate sizes, so that at least one gauge will match each intra-moiety distance, for each pair of moieties. Alternatively or additionally, at least two gauges or gauge sides are similar in moiety geometry. Alternatively, only two gauge sides match. Different environments may dictate a different number of gauges, for example, some bonds may exhibit more flexibility at one temperature, but not at another.

The sampling of distances by the gauges may be even along the range or it may vary, for example being exponential and/or stepped, due to the effect of the changing scaffolds between triangles, to achieve different triangle side lengths.

It should be noted that some sets of side lengths cannot be combined in a single triangle, due to the required relationship in a triangle, namely, that the sum of lengths of any two sides be greater than the length of the third side.

13.6 ENVIRONMENTAL STABILITY

In an exemplary embodiment of the invention, the gauges are applied to the target under normal physiologic conditions, including controlled pH, temperature and ionic content. They may thus be selected to perform correctly only in the standard environment.

However, in some embodiments, the testing range may not match the physiological conditions normally present. In a particular example, a desired property of a drug may be activity at hyperthermia temperatures or for patients with a fever and not at normal physiological temperatures.

A special set of gauges may be used for non-physiological conditions, for example replacing some gauges with others. Alternatively or additionally, a relatively stable set of gauges may be provided, which exhibit a same behavior over a wide range of environments.

Alternatively or additionally, even if the gauge properties change, if the change is known and spanning is retained, the reconstruction method may be adjusted (e.g., the locations and/or amplitudes in triangle space) to account for environmental effects.

Another possible environmental variable is the type of solvent used, as some gauges may not be very soluble in water, so assaying may use non-standard solvents.

In another example, the target may exhibit conformal changes, which are desired to be measured, under small changes in the environment, such as the concentration of calcium ions. It may be desirable that the gauges do not exhibit the same sensitivity as the target protein to the changes.

Alternatively or additionally, the gauges may be designed or selected to change in different environments, thus, for example, allowing a single gauge to make multiple measurements, each at different environments.

13.7 UNIQUENESS OF GAUGES AND OVERLAP OF SIDES AND TRIANGLES

As alluded to above, two different gauge-sides lengths may match a particular interaction location configuration, for example, by an interaction location being capable of binding to two different moieties and/or due to flexibility in the gauges (and/or the target), which cannot be completely eliminated.

In an exemplary embodiment of the invention, the overlap between gauge measurements is controlled to be substantially constant over the gauge space. Alternatively or additionally, the overlap is minimized. Alternatively, at least a minimum amount of overlap is encouraged, for example to compensate for various eventualities where a gauges does not bind or an assay fails or to provide additional linking information.

It should be noted that even if substantially rigid gauges are used, there is a level of tolerance inherent in the interaction, so that some freedom is always available, albeit, possibly at the expense of binding strength.

If the degree of overlap is known, its effects can be compensated for in the above reconstruction method, for example during clustering. Alternatively or additionally, if an expected degree of overlap does not exhibit expected effects, the measurement is suspect.

In an exemplary embodiment of the invention, however, a large degree of overlap is provided, for example a factor of two, three or more repetition of triangles. Fractional overlap may be provided, for example, by using moieties that have non-orthogonal affinities (in the detectable range) and/or as a result of partial overlapping between triangles. Generally

however, an exactly same triangle will not be repeated, for example, due to differences between scaffoldings and/or effect of other moieties within a scaffolding.

Thus, alternatively or additionally, to accidental overlap, some or all triangles are repeated between gauges. In an exemplary embodiment of the invention, this repetition is used to compensate for the effect of steric clashes and/or other unexpected chemical behavior exhibited by some of the gauges. Alternatively or additionally, the repetition is provided to assist in determining which triangle bound, based on the binding of gauges. To this effect, the gauges may be selected so that there is a lesser overlap between gauges with respect to the other triangles the two gauges include. It appears, however, that if the scaffolds are sufficiently different, the probability of most of the triangles in one scaffold overlapping with most of the triangles in another scaffold is small. This may assist in distributing the overlapping between different scaffolds and gauges. Alternatively, similar scaffolds may be used, so that a greater degree of overlapping of triangles of same gauges may be provided. It should be noted that part of the overlap is provided by the fact that the gauges may have some degree of flexibility, so a same triangular array of binding points can be matched by triangles of different sizes. In one exemplary embodiment of the invention, the library is designed so each triangular array of points can be matched by at least one larger triangle and at least one smaller triangle. This overlap may be in addition or instead of repetitive type overlap where a substantially same triangle is provided at least twice.

Optionally, the order of moieties in a particular scaffold is controlled to account for expected steric clashes, for example, to assure that at least some triangles will not have the same steric clash problems as other triangles.

Alternatively or additionally, a mixture of gauges, having same triangles, but different expected steric clashes may be mixed in a single assay, to help avoid the steric clash problem.

In an exemplary embodiment of the invention, while triangle overlap in general and are not exactly the same, the gauge triangles of at least some of the library, for example, 20%, 40% 60% or any smaller intermediate or larger percentage, are selected so that distribution of triangles in triangle space forms a relatively discrete grid, with clusters of triangles near grid points. Alternatively, at least some of the library, for example, 20%, 40%, 60% or any smaller, intermediate or larger percentage, is selected so that the coverage of the triangle space is relatively uniform, with less clustering. As noted above, overlap may be useful to overcome various causes of non-binding. However, greater overlap may mean a larger library.

It should be noted that overlap degree need not be uniform. For example, certain triangle sizes may be more prone to steric clashes (e.g., if they all use large scaffolds), in which case a greater overlap may be provided. Optionally, the clustering methods take the degree of overlap into account, for example to determine a threshold for deciding if a triangle was

5   bound.

13.8 GAUGE MASS AND SIZE

In an exemplary embodiment of the invention, the gauges are selected to have a minimal mass. It is expected that as mass increases, a gauge is more energetic and less likely to bind. Alternatively or additionally, greater mass often means greater size and more chance for

10   steric clashes. In an exemplary embodiment of the invention, the scaffolds are selected to have a mass under 200, not including moieties. Possibly, the increases mass of benzene ring moieties is offset, at least in part by their enhanced affinity. Alternatively or additionally, gauges are selected by size, for example to be no larger than 4 fusen rings in size (e.g., about 10 Å). Alternatively or additionally, when selecting a molecule for inclusion as a gauge, the

15   selection is failed if the molecule is too large or too massive. It should be noted that in some case, the size considerations are relative. For example, it is desirable in some embodiments of the invention that a triangle have sides on the order of a size of a scaffold. Small triangles on a large scaffold may be ignored when considering the triangles contributed by a particular gauge, and possibly forced to be provided by a smaller scaffold.

20   It should be appreciated that these examples are not limiting and a gauge may be larger and/or have a greater mass or be limited to be smaller and/or have a smaller mass, depending on the application or implementation, for example.

14. PARTICULAR AND GENERAL GAUGE SET DESIGN

14.1 EXAMPLE SPANNING LIBRARY SIZE

25   Under certain assumptions, the following is an estimation of the number of gauges and triangles in a complete spanning library for small molecules on protein targets.

Assuming the range of lengths to be covered is 9 A°, at steps of 1 A°, the number of possible triangles is 10*10*10/(2*3) (factor of 2 for triangle in equality and factor of 3 for rotational degeneracy. Assuming 10 moieties and moiety directions, gives about 166,000

30   triangles. Assuming an overlap factor of 3 and 5 triangles per gauge, gives about 100,000 gauges. These numbers are of course only exemplary, but may serve to clarify the following description of library design.

It can be seen that the size of the library depends on the triangle space to be spanned, the degree of accuracy, complexity of gauges and the degree of overlap. Any of these may be varied in accordance with exemplary embodiments of the invention, for example, yielding libraries with between 10,000 or fewer gauges and 1,000,000 or more gauges. Exemplary

5   intermediate library sizes include 30,000, 60,000, 80,000, 200,000 and 550,000 gauges. In addition a library may include non-gauge elements or may form part of a much larger screening library, for example as described above. In general, the more gauges in a library the more work it is to apply as a whole. However, greater accuracy, specificity and coverage may be available as the library size increases.

10   An example of smaller gauge libraries, are those that have only 7 moieties, reduce the sampling distance to 8 and/or reduce the overlap factor to 2. Smaller and larger libraries and/or other modifications of library parameters, can also be provided in some embodiments of the invention, as well as various partial libraries.

In another example, all gauges are designed to include a single triangle (or a small

15   number), in which case about 166,000 gauges are needed (if there is no overlap). In such a specific-gauge library, the initial clustering step is optionally omitted. However, it is noted that gauges will generally include, at least inadvertently, more than one measure, so that clustering may still be useful. In some cases, a moiety is provided on a gauge to prevent the scaffold part of the gauge from participating as part of a measure and/or to reduce the number of different

20   triangles provided by a particular gauge.

14.2 GAUGE SUBSET SELECTION

A particular type of gauge library is a subset library, which may be smaller than a standard library (but it may be larger, for example, if it has a higher resolution of lengths and/or moiety types).

25   In an exemplary embodiment of the invention, only a subset of all the gauges are used for a particular measurement. In some cases this is because of the use of an iterative approach, which does not use all the available gauges at every step. Alternatively or additionally, it may be desired to reduce the number of assays performed. Alternatively or additionally, this may be the result of a large overlap between different gauges. In an exemplary embodiment of the

30   invention, gauges are selected to better operate in an environment (e.g., temperature, pH, solvent used) and/or exhibit fewer adverse interactions with the target and/or the assay, for example, in a cellular assay. Alternatively or additionally, this may be the result of a failure to

create a complete spanning library, for example as shown in the example above which may be nearly universally useful for all protein targets of small drugs.

It should be noted that one potential advantage of rigid gauges is that the geometry of many rigid molecules is minimally affected by environmental changes, even if their chemical behavior is affected. This may allow the gauge set to be more universal.

In an exemplary embodiment of the invention, gauges for the subset are selected based on the target type, for example, the expected range of distances between the interaction locations.

Alternatively or additionally, the gauges are selected responsive to a measurement need. For example, if a certain interaction location has an unknown size but is known to have a weak affinity, a denser sampling of the moiety size range may be used for that interaction location (e.g., for gauges that are expected to bind to that location).

Alternatively or additionally, the gauges are selected responsive to knowledge of the available drug types, for example, the types of possible hydrogen bond directions in the drug. Alternatively or additionally, the gauges are selected to better distinguish between two potential drugs, by providing better resolution for the differences between the drugs.

In some embodiments of the invention, the gauges are selected so that an approximately correct model can be reconstructed, even for those parts of the target for which lower resolution gauges are used. Alternatively, the gauges are selected to determine if a certain drug should bind to the target, so only gauges required for measuring a smaller range of possible configurations are necessary.

Optionally, the gauges are selected responsive to a desired type of bond matching, for example, if the target and/or potential drug is known to include sulfate bonds, gauges including sulfate moieties are used.
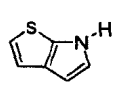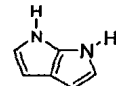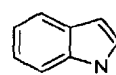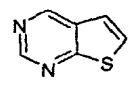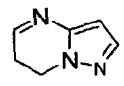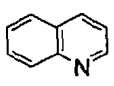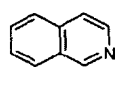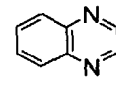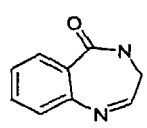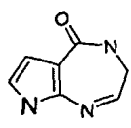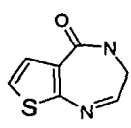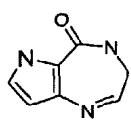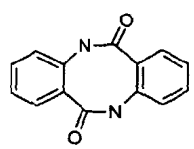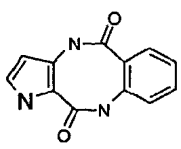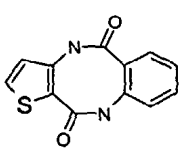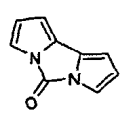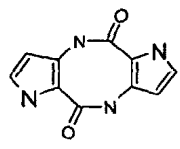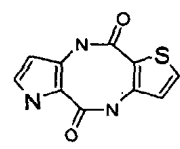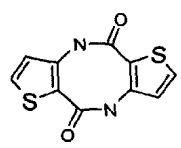
In an exemplary embodiment of the invention, a method of selecting a gauge subset comprises:

(a) determining a use of the gauge subset;

(b) determining a rule or rules for selection of gauges to meet said use (e.g., sizes, moieties, densities, etc., e.g., as above);

(c) selecting from the library a plurality of gauges that meet said rule(s); and

(d) optionally, determining if the resulting library is likely to provide the desired information for said use. For example, a simulation may be made to see if the assay results are likely to result in a reconstruction (e.g., based on assay binding rate, density of coverage,

properties or target and/or degree of overlap required to distinguish between triangles on a gauge). In another example, the information is partial information and a simulation is run to see if the information can be distinguished.

14.3 GAUGE LIBRARY DESIGN

The following table shows an exemplary set of scaffolds for a gauge library design:

AutoNom Name:
Thiophene

AutoNom Name:
1H-Pyrrole

AutoNom Name:
Furan

AutoNom Name:
Benzene

AutoNom Name:
Pyridine

AutoNom Name:
Pyrimidine

AutoNom Name:
Pyrazine

AutoNom Name:
6H-Thieno[2,3-b]pyrrole

AutoNom Name:
1,6-Dihydro-pyrrolo[2,3-b]pyrrole

AutoNom Name:
1H-Indole

AutoNom Name:
Thieno[2,3-d]pyrimidine

AutoNom Name:
6,7-Dihydro-pyrazolo
[1,5-a]pyrimidine

AutoNom Name:
Quinoline

AutoNom Name:
Isoquinoline

AutoNom Name:
Quinoxaline

AutoNom Name:
3,4-Dihydro-benzo[e]
[1,4]diazepin-5-one

AutoNom Name:
3,8-Dihydro-4H-pyrrolo
[2,3-e][1,4]diazepin-5-one

AutoNom Name:
3,4-Dihydro-thieno[2,3-e]
[1,4]diazepin-5-one

AutoNom Name:
3,6-Dihydro-4H-pyrrolo[3,2-e]
[1,4]diazepin-5-one

AutoNom Name:
5H,11H-Dibenzo[b,f][1,5]
diazocine-6,12-dione

AutoNom Name:
1,4-Dihydro-10H-1,4,10-triaza-benzo
[a]cyclopenta[e]cyclooctene-5,11-di
one

AutoNom Name:
4H,10H-1-Thia-4,10-diaza-benzo[a]cy
clopenta[e]cyclooctene-5,11-dione

AutoNom Name:
Dipyrrolo[1,2-c;2',1'-e]
imidazol-5-one

AutoNom Name:
1,4,7,9-Tetrahydro-1,4,6,9-tetraaza
-dicyclopenta[a,e]cyclooctene-5,10-
dione

AutoNom Name:
4,7,9-Trihydro-1-thia-4,6,9-triaza-
dicyclopenta[a,e]cyclooctene-5,10-d
ione

AutoNom Name:
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ene-5,10-dione
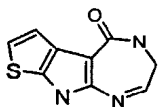
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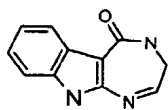
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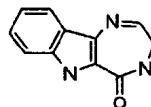
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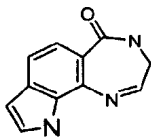
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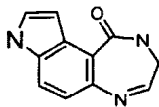
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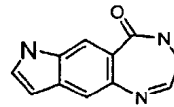
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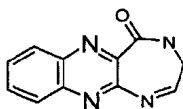
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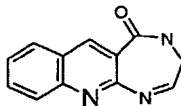
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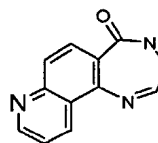
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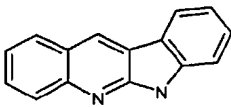
AutoNom Name:
11H-10,11-Diaza-benzo[b]fluorene

AutoNom Name:
α-hydroxyacids

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α-aminoacids
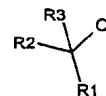
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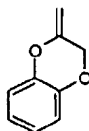
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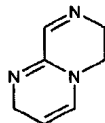
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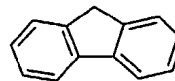
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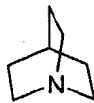
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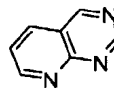
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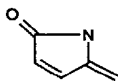
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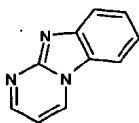
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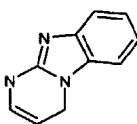
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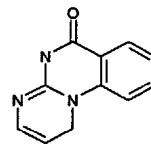
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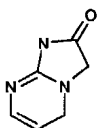
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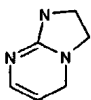
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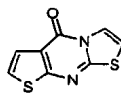
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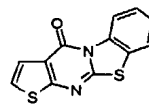
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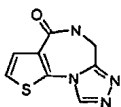
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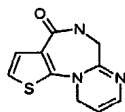
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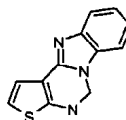
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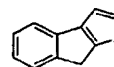
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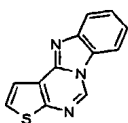
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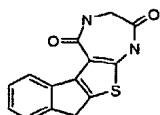
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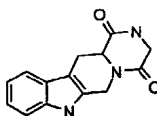
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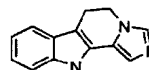
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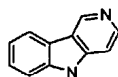
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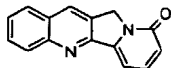
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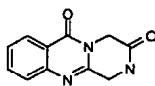
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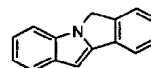
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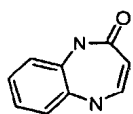
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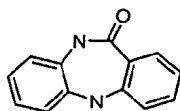
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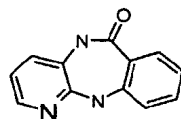
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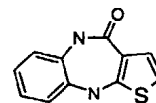
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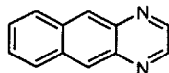
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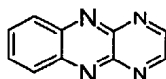
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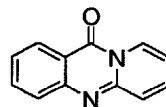
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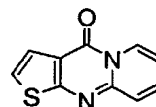
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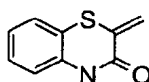
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TABLE I

In an exemplary embodiment of the invention, the moieties are Me (methyl), Et (eteyl), Pr (propyl), Ph(phenol), CO_2H, OH and NH_2. Although the moieties may be connected at any of the R locations, not all the possible gauges are needed, as explained above. The indolizine scaffold can have, at R1, either COOH or NH_2, both of which are shown in the table. In particular, applicants have found that in general, a scaffold with four or five attachment points can span its entire range of triangles with M moieties, using only about M^3 different gauges. This is believed to be generally true (e.g., the exponent is not much higher than 3) for scaffolds with a larger number of attachment points.

It should be noted that even if a library does not cover all the possible triangles, a viable reconstruction is still possible for many drug targets and/or considerable utility attached to the library. Also, as noted above, partial reconstruction is useful in some cases. Also, as noted above, gauge matching can be used as leads and/or to reject leads, even if no reconstruction is possible, in some cases. In some embodiments of the invention, a failure of the method is typically self-evident and does not create an unproductive search after non-existent leads.

Alternatively to constructing a library of gauges from scratch, at least part of the library can be generated by scanning existing libraries for molecules that include triangles having

desired sizes and/or moieties. Optionally, molecules that are small and rigid are selected, as described above. This type of library, for example, may not be based on a set of scaffolds.

14.4 LIBRARY BUILDING METHOD

From the above description, it should be clear that there are many methods that may be used to construct a library. The following exemplary method is described, at least partly to illustrate various applications of the above rules:

(a) determine library parameters: e.g., spanning range and accuracy desired for library;

(b) select moieties for library;

(c) select a scaffold;

(d) generate gauges from the scaffold;

(e) add generated gauges if they are suitable;

(f) repeat (c)-(e) until the library spans the range with a desired accuracy and/or coverage; and

(g) optionally, check library.

In accordance with example embodiments of the invention, a resource allocation algorithm is used, for example the greedy method or the first fit method. These names refer to methods of selecting from a set of possible resources, which resource to allocate at a particular time, for example, which gauge to choose for a library from available gauges on a scaffold or which scaffold to add to the library. Many such methods are known in the art and may be used, noting that the method is not required, in some embodiments of the invention, to provide an optimal solution, just a working or reasonable solution.

An alternative method is a selection-based library construction method. In this method, existing molecule libraries are scanned for molecules that have gauge-like properties (e.g., as described herein). The resulting potential gauges may be filtered out to remove redundancies. It is expected however, that in the current state of public libraries, scanning such libraries will not yield a complete gauge library. Optionally, such a selected gauge library will be completed using other techniques, such as scaffold based gauge generation.

It should be appreciated that given a large number of possible gauges and a smaller actual required number, there are many optimization techniques for selecting a suitable and/or optimal set of gauges that meet the required number. As noted above, the selection may be based on the use to which the library is put and/or be based on considerations such as diversity, chemical behavior and ability to synthesize. In addition, a part of a library may be replaced, for example with a set of gauges constructed from other scaffolds or using molecules selected

from a library of potential leads. In an exemplary embodiment of the invention, at (g) a constructed library is optimized, for example, removing redundancies and ensuring that desired distributions (e.g., of triangles, chemical properties) and overlaps (e.g., of lengths and/or moieties) meet certain guidelines and/or are optimal.

14.5 SCAFFOLD SELECTION METHOD

In an exemplary embodiment of the invention, scaffolds in general are selected to have certain desirable properties, for example, one or more of:

(a) small size;

(b) rigidity;

(c) suitability for combinatorial chemistry;

(d) including a plurality of attachment points, for example, 3, 4, 6, 10, 12 or any smaller intermediate or larger number, for attaching moieties and/or chemical markers (e.g., for binding assays, chemical manipulation);

(e) a geometric arrangement of the attachment points so that a range of triangle sides can be provided;

(f) 3D structure, for example planar or volumetric may be preferred for different situations;

(g) number of excess protrusions (in some cases may be desirable to be small), to which moieties may or may not be attached, so that excess is relative to a perfect scaffold where the useful (e.g., for the library or for a particular triangle) moieties define the shape of the scaffold; and/or

(h) solubility (may be determined, for example, based on the number of polar atoms in the scaffold).

In general, as more attachment points for moieties are provided, the scaffold is more able to provide triangles of various sizes, however, this may adversely affect the scaffold (and gauge size) and many of the triangles may be useless. In a scaffold in general, it may be useful to designate only some of the potential attachment points as attachment points to be used. This may reduce the number of different synthesis methods used and/or promote uniformity thereof.

Not all or even any of these properties are essential in some embodiments of the invention. As a practical matter, small rings and ring chains appear to meet these criteria. Thus, in an exemplary embodiment of the invention, a set of scaffolds may be generated by reviewing existing known rings and small chains for molecules that meet the desired criteria. In an exemplary embodiment of the invention, during this type of selection an effort is made to

select scaffolds having a range of sizes (e.g., distances between attachment points), so that a range of triangles may be generated using the scaffolds.

In addition to scaffold criteria in general, a selection of scaffolds for a library may impose other criteria, for example that the scaffolds generate a spanning library of gauges

5   and/or a range of chemistries and/or require a relatively small number of relatively low complexity process to generate the gauges.

In an exemplary embodiment of the invention, the scaffold selection process is as follows. Given an existing library portion, a new scaffold is selected from a list of available potential scaffolds if it answers at least one of the following criteria:

10   (a) the scaffold generates a large number of triangles that are missing from the libraries, for example, 10, 50, 100 or any smaller intermediate or larger number, such as a user set number;

(b) the scaffold generates at least one (or a small number of triangles, such as less than 20, less than 10 or less than 5, or any other user set value) triangles that have evaded

15   generation using other scaffolds and form missing portions of the library;

(c) the scaffold has a significant amount of known chemistry (e.g., methods for manipulation and/or adding moieties); and

(d) the scaffold adds the potential for a desired amount of overlap.

In general, if a larger the number of gauges is produced, it may be easier to complete a

20   library. However, not all scaffolds can generate large numbers useful triangles.

It should be noted that in some divergence based methods of library design, each library element is selected to be as different as possible, so that this type of selection methods and/or at least some of the criteria used cannot be applied and run against conventional ideas.

It should be noted that as the library fills up, consideration (b) may be given more

25   weight, with the possibility of searching or constructing a scaffold that has the desired properties (e.g., to form required triangles). Further, the search may lead to selection of less rigid scaffolds, for example, to ensure coverage or due to lack of suitable more rigid scaffolds.

In an exemplary embodiment of the invention, during an optional optimization stage of the library, scaffolds are assessed as to their quality (e.g., meeting scaffold criteria), number of

30   triangles generated and/or uniqueness of triangles generated. A scaffold may be removed from the library if it is determined to be less useful or unneeded based on one or more of these considerations.

One difference between scaffolds is the number of rings in a scaffold. In general, as the number of rings increases, so does the scaffold size and weight. For some applications, the number of rings in a scaffold may be used as a heuristic to determine what approximate triangle sizes the scaffold can provide. For some applications, multi-ring scaffolds may be

5   necessary. Alternatively or additionally, single or bi-ring scaffolds may be useful for small triangle sand/or for reducing steric clashes.

14.6 GAUGE SELECTION METHOD

In an exemplary embodiment of the invention, gauges in general are selected to have certain desirable properties, for example, one or more of:

10   (a) small size;

(b) large numbers of triangles;

(c) high or otherwise desirable binding affinity, for example in the range of 1-100 micro Molar;

(d) rigidity;

15   (e) the attached moieties defining the volume of the molecule;

(f) relatively uniform binding probability for all moieties, for example a factor of ten between moieties and a factor of 100 between molecules in a library, however, in other embodiments other, smaller or greater factors (e.g., ~1, 5, 20, 50, 130, 250, 1000 or any smaller, intermediate or greater factor) may be provided for one or both criteria; and/or

20   (g) chemical behavior, such as (i) solubility, for example in a natural solute of the target (or an approximation thereof), for example water at a given pH, with some detergent such as DMSO to aid solubility, (ii) lack of reactivity with expected contaminants, (iii) lack of chemical reactivity (creation of covalent bonds) with a target protein i.e., with amino acids or known typical combinations of them and/or with a substrate, (iv) desired behavior over a range

25   of properties.

In general, a higher uniformity of binding means that the assays have a same meaning. However, it is generally not practical to provide such narrowly defined materials, and a certain latitude is useful if a realistic set of chemical is to be provided.

When generating a library (or part thereof) by selection of gauges from existing

30   molecule screening libraries, each molecule is, for example screened against the desired criteria. A molecule may be selected or rejected. Alternatively or additionally, a molecule may have a score of suitability associated with it. Similarly, a set of potential gauges may be generated from scaffolds.

In an exemplary embodiment of the invention, gauges are selected from the generated/selected set, based on one or both of suitability (e.g., relative or absolute) and meeting of group criteria. In an exemplary embodiment of the invention, one or more of the following group criteria are applied, for example as binary criteria or as part of a score:

(a) That uniqueness of the triangles provided and/or them matching missing triangles.

(b) Matching of flexibility of the gauges and/or individual triangles, to desired flexibility.

(c) Shape of gauge as a whole, for example, being elongate or being round. The shape may be a consideration, for example when building a library in which shapes are varied so that steric-clashes will not reject all of a certain triangle. To this end, the shape of the gauge may interact with the location of specific triangle son the gauge, e.g., if a same triangle is found on two elongate gauges, it may be desirable that on one of the gauges the triangle is in an axial direction and in the other, in a trans-axial direction. Alternatively or additionally, shape considerations relates to the three-dimensional shape of the gauge and/or relative layout of triangles in the gauge.

(d) That certain non-triangle measures are found, for example specific non-triangle measures or that a uniform (or other) distribution of such 4- 5- or other multi-point measures are provided.

It should be noted that for gauges and/or scaffolds, the determination of suitability may include, for example one or more of using simulation and molecular analysis software, chemical laboratory testing and/or searching literature for the same or similar chemicals.

The above selection method may be useful when designing a single universal library (or a set of such libraries for broad uses). It should be noted however, that some, similar or other selection methods may be used when generating personal and/or ad-hoc libraries, searching for gauges or measures with particular properties and/or when defining a gauge and/or scaffold to be generated.

14.7 GAUGE SYNTHESIS

The generation of a gauge library from scaffolds, in some embodiments of the invention, may assist in the serial synthesis of the gauges. In libraries that are not (or are partially not) scaffold based, standard synthesis methods may be used.

In an exemplary embodiment of the invention, the gauges are synthesized, for example using liquid phase methods as described below, and impurities are removed using standard methods, for example using HPLC.

91

In an exemplary embodiment of the invention, a parallel synthesis method is used, in which a plurality of gauges are synthesized at once and then separated. It should be noted that in some embodiments of the invention, only a small number of the gauges that can be created by a scaffold are actually needed. Alternatively or additionally, even if many of the particular gauges cannot be created, a sufficient number of alternative gauges may be available, to provide spanning and/or overlap of a desired triangle space. For example, on a five point scaffold with 10 moieties, 100,00 combinations are possible, of which 1000 are sufficient cover all the triangles. Thus the choosing can be, for example, ad hoc, such as based on the actual yield (e.g., relative yield) or based on the prior design of the library.

In an exemplary embodiment of the invention, combinatorial chemistry methods are used to attach moieties, each at a different attachment point of a scaffold, optionally so that all combination of moieties are created. Each final compound is made attached to a polymer bead (for example) for ease of separation. The beads may be color coded for assistance in separation and/or identification of the created gauge.

Alternatively, other solid phase methods, for example as described below or as known in the art, are used.

14.8 MIXED LIBRARY DESIGN

As noted above, in order to be useful, a complete universal library is not required. Further, a gauge library may be included into a "regular" screening library. In an exemplary embodiment of the invention, at least 0.05%, 0.1%, 0.5%, 1%, 5%, 10%, 20%, 40% or any smaller, intermediate or larger percentage of the molecules in a library used for screening, measuring and/or other uses comprise gauge-like molecules. Of such gauges, for example, less than 50%, or greater than 30%, 60%, 80%, 90%, or any smaller, intermediate or larger percentage of the gauges are scaffold-based gauges, where a scaffold is used to generate at least 5 gauges with less than 20% overlap in triangles defined by attached moieties. As noted above, while a library may include standard screening parts, providing significant numbers of gauge-like molecules may assist in applying the methods described herein.

In an exemplary embodiment of the invention, the library comprises at least 5,000, 10,000, 20,000, 50,000, 80,000 ,100,000 or any intermediate or greater number of gauges. These gauges may be, for example, scaffold based gauges, plain gauges and/or rigid gauges. These gauges may span, for example, 5%, 20%, 40%, 80%, 100% or any smaller, intermediate or greater percentage of the triangle space, for example, with an overlap of 1.1, 1.5, 2, 3 or any smaller, intermediate or greater degree. As noted above, when spanning is better, the degree of

success may be higher, albeit at a cost of using a larger library. Smaller libraries may be easier to apply and still yield useful results, in many cases.

One significant difference between gauges and other lead libraries (e.g., diversity based libraries), in accordance with some exemplary embodiments of the invention, is that a relatively large number of matches is expected using gauge based libraries. For example, at least 0.01%, 0.05%, 0.1%,0.2%, 0.5%, 1%, 3%, 5%, 10% or any smaller, intermediate or greater percentage of numbers is expected to bind. The percentage of binding may depend, for example on the ratio between gauges and non-gauge leads in a library.

It should be appreciated that these percentages are not mere numbers. Rather, they represent a qualitative difference from libraries where more often than not, no leads bind. The greater the probability of finding one or more leads and the greater the number of leads, the more likely it is that a drug will be found. However, of binding is too likely, the quality of information provided by the binding may be reduced.

A library may also include a mix of three-point measures and higher valance measures. While any gauge that includes more than three moieties includes a high valance measure, in an exemplary embodiment of the invention, the library is designed to span the higher valance space. For example, the library spans at least 0.1%, 0.3%, 0.5% or at least 1% or any smaller intermediate or larger percentage of the space of the higher valance measures. The spanning may be, for example, continuous (e.g., the whole library at a low resolution or part of the library at a high resolution) or it may be discrete (e.g., isolated parts of the library). In general, higher valance measures may require a very large number, for example, 20,000,000 for a spanning equivalent to the 100,000 library of the triangles, so commercial implementation may depend on the availability of even more parallel assays than available today. Optionally, the higher valance measures are provided to be more flexible, so that a lower resolution is required to span the space.

14.9 ENSURING LIBRARY RELIABILITY

In an exemplary embodiment of the invention, once a library is constructed and/or during its construction, various quality assurance processes may be employed. In one example, the library is analyzed to ensure that it meets the spanning, overlap and/or accuracy criteria set for the library. Any missing triangle and/or gauge may be provided at this point or noted as missing. Alternatively or additionally, molecules with low solubility or high toxicity are removed and/or replaced with molecules exhibiting similar spatial chemical configurations.

In an exemplary embodiment of the invention, feedback from use of the library is used to calibrate the library, reconstruction process and/or to assist in library design.

In an exemplary embodiment of the invention, the theoretical modeling of the library is compared to its actual behavior, for example, by running test assays against randomly selected targets having a known and/or an unknown structure. Two examples of molecules with known structures are thoroughly mapped proteins and structures constructed from DNA or RNA, with optional attached elements. Optionally, the targets are not random and are selected to test certain assumption in the theoretical model of the library. Alternatively or additionally, the calibration is provided by analysis the results of real uses of the library over time.

In an exemplary embodiment of the invention, one or more of the following data is provided by such analysis:

(a) assay binding rates for gauges and families (e.g. similar) gauges;

(b) dependency between environmental conditions and binding rates and/or conformal changes for one or more gauges;

(c) Baysian probability of steric clashes between gauges (and triangles thereof) with overlapping triangles;

(d) actual degree of overlap between triangles;

(e) dependency between target type and gauge binding; and/or

(f) parameter values (e.g., thresholds) for the various algorithms.

Other properties of the library, for example general rigidity of the gauges and correctness of values in the data bank may also be provided by such or other analysis.

In an exemplary embodiment of the invention, as a result of the above findings, the library is amended, for example, by removing redundant gauges and/or searching for gauges to generate the missing triangles.

Alternatively or additionally, as a result of the above findings, later generation of libraries and sub-set libraries is modified to take the calibration information into account, for example in a specific manner as relating to specific gauges and/or in a general manner as it relates to statistical deviation of the behavior of scaffolds and/or families of gauges from their appropriate theoretical models and/or as parameters for such models.

Alternatively or additionally, the reconstruction process is calibrated, for example to better distinguish which triangle matched, the actual coverage of each triangle, the spatial shape (in triangle space) of a match and/or the relative binding strength of various triangle measures and/or gauges.

14.10 HUMAN INTERACTION DURING LIBRARY DESIGN

The process of designing a library may be automatic, semi-automatic or manual. In general, when more potential gauges and/or scaffolds are available and suitable modeling software is available as well, automated designing may be provided. one example of this is

5 once a complete library is available, selecting a sub-set may be completely automatic, once the desired parameters are provided. Some of the library may be generated automatically in any case, for example selection of gauges from existing libraries and/or selection of scaffolds from existing libraries. The determination of ease of synthesis may be required to be manual if no earlier information is available. It is noted, however, that in an exemplary embodiment of the

10 invention, the scaffolds are chosen to have known chemical behavior and synthesis paths, so that attachment of moieties should require little or no research work. In some cases, however, a human may be required to not only select between alternatives but actually to find a particular missing gauge or suggest a scaffold design. It is noted, however, that the mathematical description of the library in accordance with some embodiments of the invention, assists and

15 may allow complete or nearly complete automatic generation of a library using constructive synthesis and/or analysis of existing molecules. Possibly, such a library may then be optimized, for example as described above, possibly manually, especially to assist in providing an easy to synthesize library.

As noted above, the reconstruction process may be completely automatic or it may

20 include a manual aspect. In general, however, it is expected that the high hit rate of binding of gauges will reduce or eliminate any need for human intervention, at least in some of the steps of drug discovery. Of course, once mapping is completed, a human user may desired to test the effect of various assumptions, for example, how the reconstructed layout depends on various assumptions made on the target conformity. Also, in some case a human expert (or an expert

25 system) may be used to select among alternative or select likely leads, since in many cases the method will generate a small number of possibilities from which one or two should be selected, failing that costs may be very high.

In an exemplary embodiment of the invention, one point for human intervention in the drug discovery process is in designing drug candidates that match a final pharmacophore (e.g.,

30 model). It is noted , that various software exists to assist or automate this step. Typically however (at this point in time), human judgment is better at assessing synthetic feasibility for complex molecules. If the suggested drugs are created by linking together gauges or simple

fragments, however, automatic assessment and possibly generation methods, may be reasonable.

15. EXPERIMENTS AND EXAMPLES

15.1 EXPERIMENT 1

5   Some of the above measurement method was testing using the following experiment.
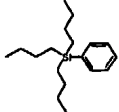
In this experiment, known inhibitors of HIV-1 Protease were analyzed to detect a set of triangle measures that should exhibit binding to HIV-1 Protease. A set of molecules including the triangle measures were selected and physically assayed and shown to have the expected binding to HIV-1 Protease. The results indicate that triangles are a viable geometrical sub-

10   structure that can be used to measure a target by binding.
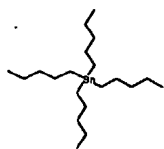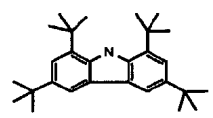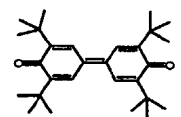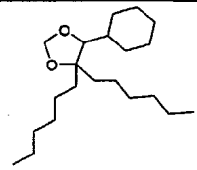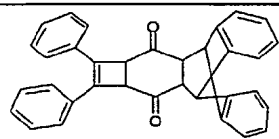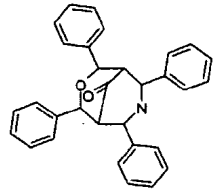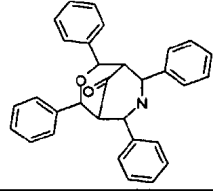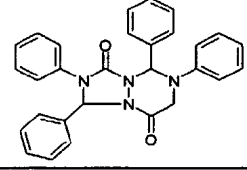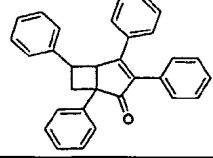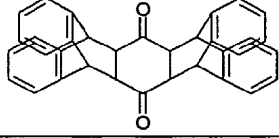
The following entries in the PDB (Protein Data Base) were extracted as structures of HIV-1 Protease with known, bound, inhibitors: 1ajv 1ajx 1dif 1gno 1hbv 1hih 1hos 1hps 1hpv 1hpx 1hsg 1hte 1htf 1htg 1hvi 1hvj 1hvk 1hvl 1ohr 1sbg 1upj 2bpv 2bpw 2bpx 2bpy 2bpz 2upj 3tlh 5hvp 7upj.
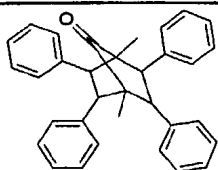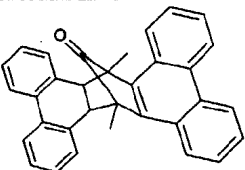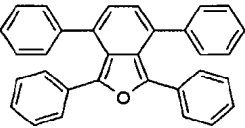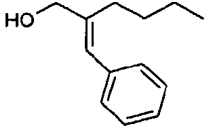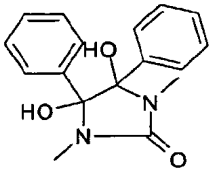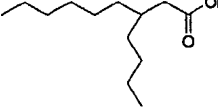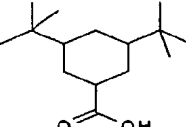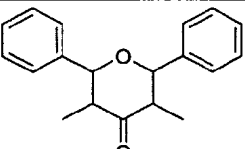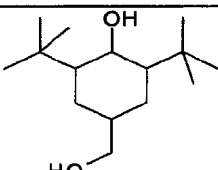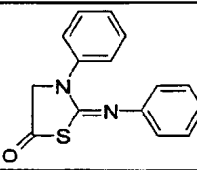
15   The structures were super-imposed using the protein as a reference frame, so that the spatial position and orientation of the inhibitors was superimposed. The inhibitor molecules were then decomposed into moieties and those were clustered in space. Strong bonding locations were identified based on the same moiety in different molecules binding to a substantially same binding location in the protease. Confidence in these locations was

20   increased by verifying that the protein moieties at those locations were compatible with the inhibitor molecule moieties.
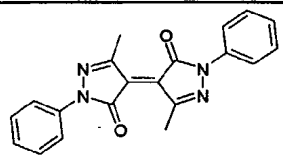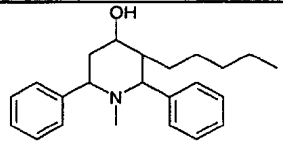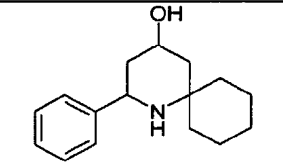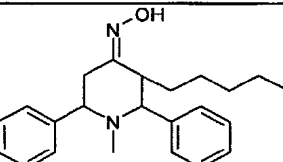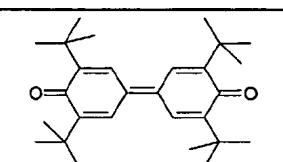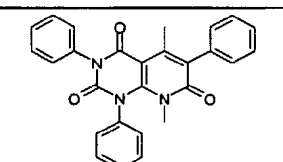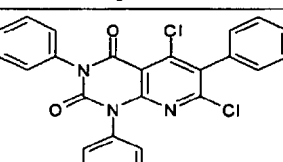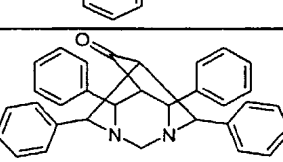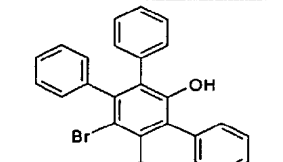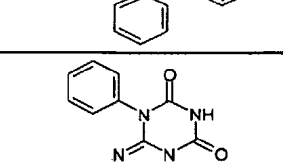
Triplets of the inhibitor moieties at the strong binding locations were selected as "triangles". Gauges, for example, of a gauge set as described above, that have those triangles, are expected to bind, or at least some of them should bind.

25   The triplets were used as a query input for a search in MDL's ACD-SC (available chemical directory for screening). Molecules that matched the queries (moieties and size) and the rigidity requirements were selected, as shown in the following table.

No.	Compound	MW	Density (g/ml)	Cat. No.	mg for 1mM in 10ml
1		276.35		S-83425-4	2.8

2		403.26	1.008	36,667-6	4.00µl
3		391.35		S-63995-8	3.9
4		408.32		S-84651-1	4.1
5		324.55		S-2210-2	3.2
6		464.56		R-15419-9	4.6
7		445.57		S-22759-5	1.9
8		445.57		S-22675-0	1.9
9		446.17		S-95285-0	4.5
10		412.53		S-9757-9	4.1
11		464.56		R-15449-0	4.6

12		438.57		R-15358-3	4.4
13		436.55		R-15353-2	4.4
14		422.53		R-33994-6	4.2
15		204.16		S-52812-9	2.0
16		298.34		S-6426-3	3.0
17		200.32	0.887	46443-0	2.26µl
18		234.34		27302-3	2.3
19		280.37		R-22433-2	2.8
20		236.36		44642-4	2.4
21		268.33		S-4228-6	2.7

22		344.38		NRB-01407	3.4
23		377.51		RJC-03605	3.8
24		245.37		JFD-03358	2.5
25		350.31		RJC-03637	3.5
26		408.63		RJC-03257	4.1
27		435.49		JFD-01334	4.4
28		460.32		RJC-02058	4.6
29		456.59		RJC-02951	4.6
30		477.41		BTB-14801	4.8
31		280.29		BTB-11623	2.8
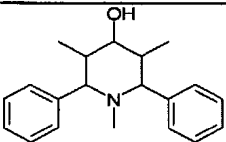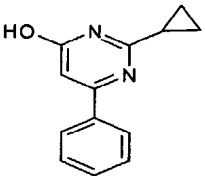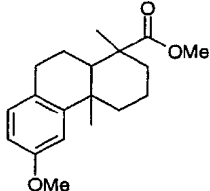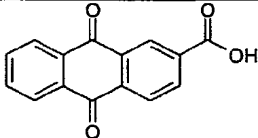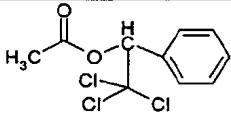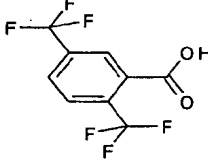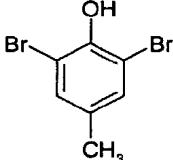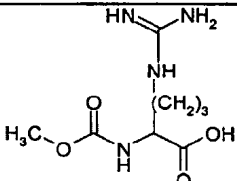
32		295.43		RJC-03631	3.0
33		212.25		RJF-00720	2.1

34		302.41		85,612-6	
35		252.23		25,272-7	
36		267.54		29,126-9	
37		258.12		23,319-6	
38		265.94		30,118-3	
39		308.34		16,263-9	

TABLE II

The molecules numbering up to 33 were expected to exhibit binding behavior, due to
them including at least one triplet. The molecules numbered 34 and up are superficially similar
but do not include the required triangles.

All of molecules were actually assayed and appeared to show activity (effect on HIV-1
Protease) at various concentrations (between 10 and 1000 micro-molar). Of these molecules 1-

33 about 60% were found to be active, in particular molecules 7, 9, 23 and 27. Also molecules 34-39 were assayed, with no activity shown, as expected.

As noted above, these results appear to indicate that gauges, in general, that have a triangle measure that matches the target layout, should, often enough, bind in a detectable manner.

15.2 EXPERIMENT 2

In this experiment, assay results performed by others were used to reconstruct the spatial layout of binding locations, for known molecules and then compared to the current state of the art.

The NCI maintains a database of molecules that have tested positive for activity against HIV. 43,000 results (in the October 1999 release) are available at "http://dtp.nci.nih.gov", under "public data", then "results from AIDS antiviral screen". From these molecules were selected a subset that showed at least a moderate level of activity and were rigid enough to allow determination of the spatial position of all their moieties. This resulted in fewer than 200 molecules. The moiety triangles in these selected molecules were clustered.

The clustering results showed a good match to the results of experiment I and the triangles of the molecules were found in the PDB structures.

These results appear to indicate that a set of gauges (e.g., the molecules that were tested for HIV) can be used to measure and then reconstruct an active area.

In addition, these results appear to indicate that at least part of a suitable library may be generated by selecting suitable gauges from available libraries, rather than by construction using scaffolds. It should be appreciated that it may not be required to determine the spatial positions of all the moieties, for example only of the moieties with a high binding affinity. Moieties with low affinities may be removed, in some cases.

16. SYNTHESIS BOOK

Following is a synthesis book, arranged in chapters, for some of the scaffolds (and gauges derived from them), shown in table I. A most important aspect of this synthesis is that it illustrates that suitable scaffolds and gauges are available and can be generated using known chemical processes applied to standard or modified sources and/or by changing their parameters in an expected manner. The references described in this book are incorporated herein by reference. In any case, the partial library described in the appendix has at least the property that is can serve in many cases to provide a partial reconstruction and/or a significant increase in lead matching.

It should be appreciated that the novel materials described in the book, the manipulation methods thereof, synthesis methods thereof and groups of molecules from this book are also considered to be within the scope of at least some aspects of the invention, for example, a library including one, two, four, six, eight or any intermediate number of scaffolds as described therein. Alternatively or additionally, a library in accordance with an exemplary embodiment of the invention, includes at least 100, 300, 500, 1000, 2000, 4000, 10,000, 20,000 or any smaller, intermediate or larger number of gauges from this book. While it is useful to select gauges from the book, for example by using the scaffolds described therein to span part of the library, this is not required.

16.1 Benzenes, Pyrimidines 6-membered ring scaffold

The Biginelli dihydropyrimidine synthesis (pathway below) is a promising multi

5   component condensation, which involves the one-pot cyclocondensation of β-ketoesters 2,

aldehydes 3, and ureas 4 providing the heterocycle 1 , which can be oxidized to the

corresponding pyrimidine moiety.
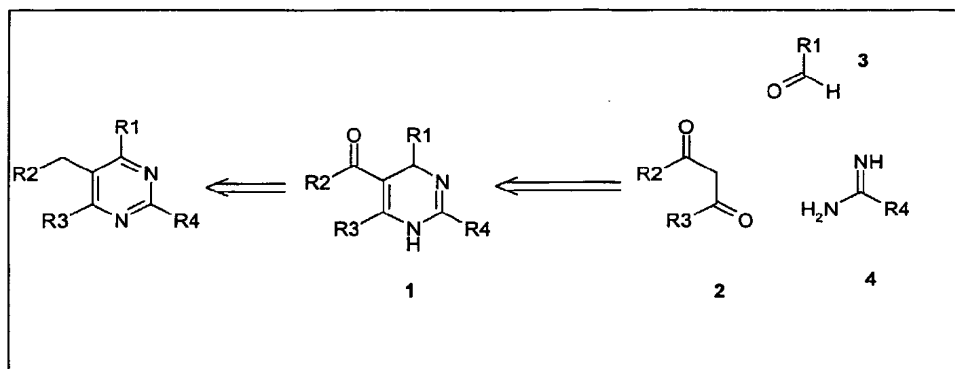
Biginelli-general multicomponent approach.

10

Several protocols have been developed for solution phase Biginelli reactions[1] In order to drive

the reactions to completion, however generally, an excess of two of the three components 2-4

has often to be employed, and purification steps are required. The solid phase synthesis

provides the desired dihydropyrimidines in good yield and superior purity directly after

15   cleavage from the resin [2] (pathway below):
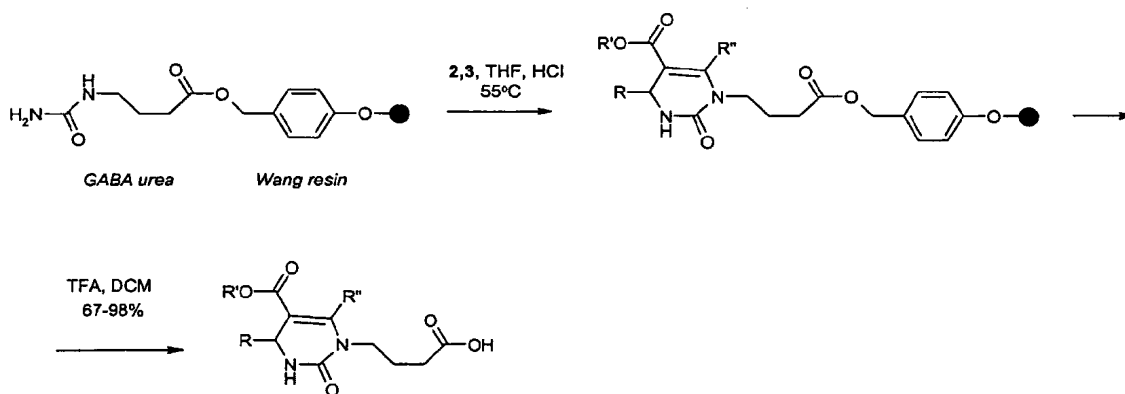
Another approach for the SP synthesis of highly substituted pyrimidines was recently

published[3]. In this work the synthesis starts from polymer-bonded thiouronium salt 5, which

undergoes cyclocondensation with acetylenic ketones **6** to form carboxy pyrimidines **7** (pathway below).
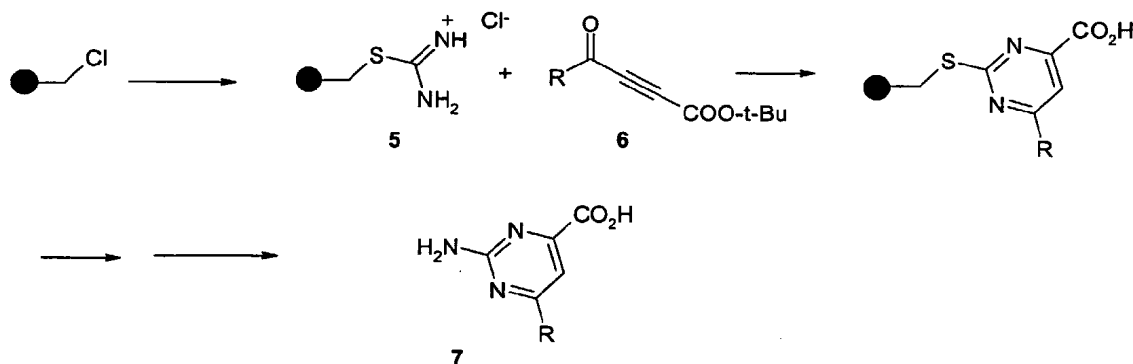
Tetra substituted pyrimidines **a** can be prepared via a modified Bigenelli's synthesis as described in the pathway below:
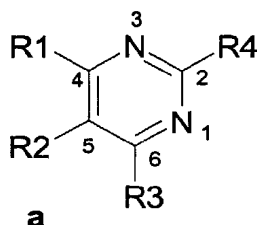
First the imidine functionalities are formed on the acid labile resin to produce the resin immobilized amidines **23**[4], urea **24** and guanidine **25**[2]. Actually, these amidines served as the first Biginelli building block. Next, the addition of the two other Biginelli building blocks, namely **2** and **3**, to **23-25** leads to generation of dihydropyrimidine scaffolds **20,21** and **22**[5,] respectively. The consequent reduction of ketone moieties (NaBH$_4$, BF$_3$OEt$_2$) leads to **14, 15** and **16,** which after cleavage (TFA, DCM, 1:1) followed by mild oxidation (CAN, CH$_3$CN) affords the desired pyrimidines **8, 9**[5] and **10** respectively. The CAN could be removed, after the completion of the oxidation, by Solid Phase Extraction (SPE) or by simple 96 well SePack. Other oxidation reagents such as MnO$_2$[6], O-chloranil [7], KMnO$_4$[8], and CrO$_3$, AcOH, H$_2$SO$_4$[9] can also be used. In case R3 = OMe (when the building block **2** is β-ketoester) dihydropyrimidines **20, 21** and **22** undergo hydrolysis of ester (LiOH, THF or 5%alcoholic KOH[10], producing the 4-carboxy –dihydropyrimidines **17, 18** and **19** respectively. Following by the same mode as for **8, 9** and **10** (1. TFA, DCM, 1:1; 2. CAN, CH$_3$CN) **17, 18** and **19** react to give the sub-library of 4-carboxy-pyrimidines **11, 12** and **13** respectively. It should be noted that in case of unsymmetrical 1,3 diketones **2** a mixture of 2 isomers are obtained.
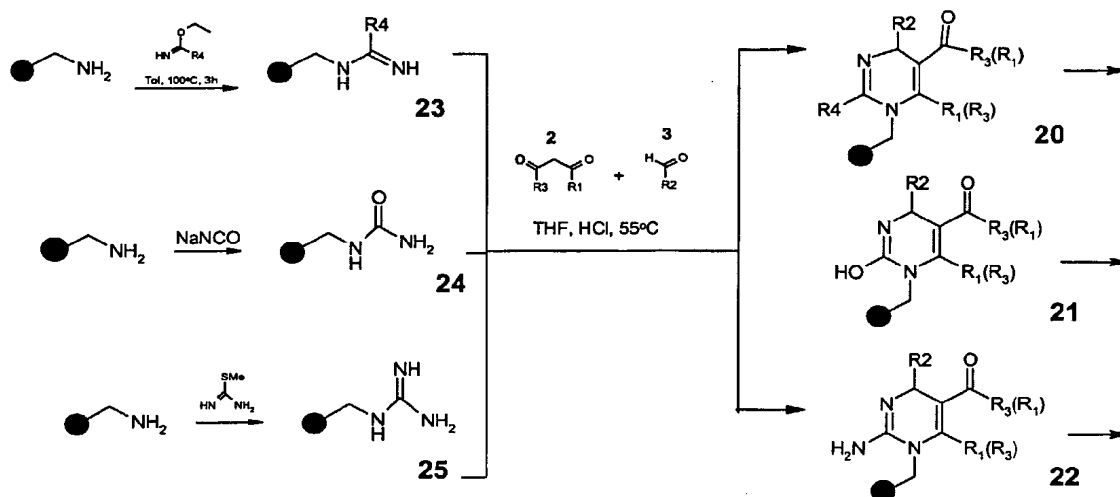
B.Chenera,WO 95/16712, 1995
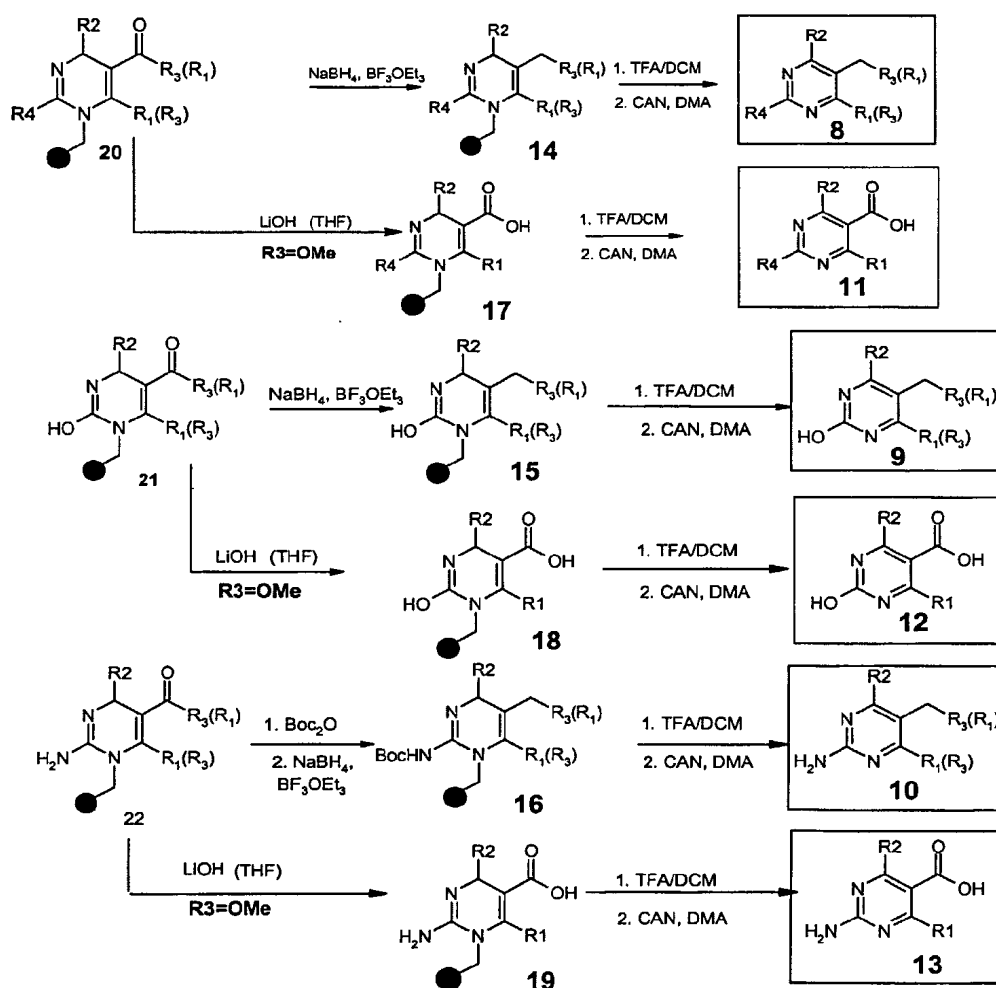
core approach towards tetrasubstituted pyrimidines.

A

It was demonstrated[11] that dihydropyrimidine 5-carboxylic acid can be transformed into carboxylic azide which in turn undergoes Curtius rearrangement to give isocyanate. This reaction provide an excess of 5-amino dihydropyrimidines A.
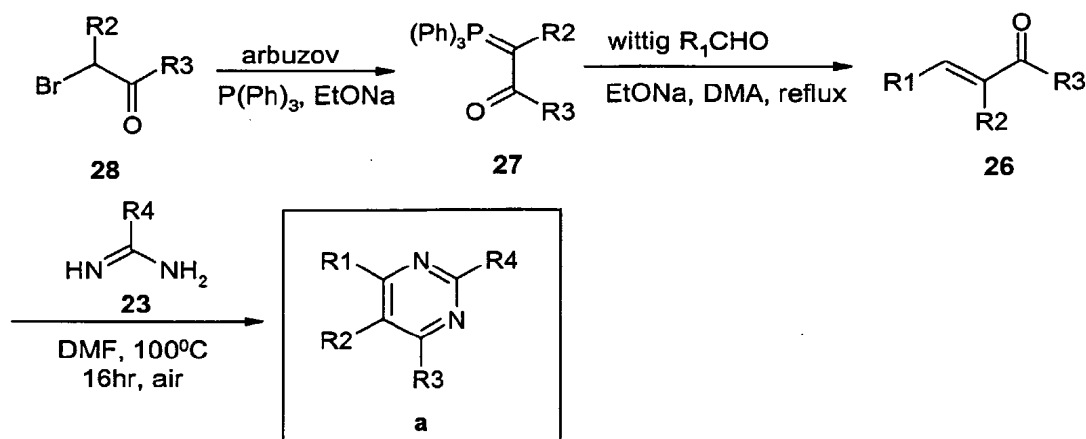
5   Pyrimidines can be prepared by cyclocondensation of amidines with α–β unsaturated ketone. Recently, the researchers have published the synthetic work[12], in which they describe the utilization of the Wittig reaction in formation of α,β-unsaturated ketones on SP for the synthesis of the various heterocycles. We propose the alternative three-step synthesis of pyrimidines **a** in solution, based on the formation of the α,β-unsaturated ketone building

10   blocks **26** as a key step [12b-d] is described below:

α–β-unsaturated ketones **26** can be obtained in good yields and purity by Wittig reaction of the appropriate aldehyde and the corresponding triphenylphosphonium bromide **27** with NaOEt at reflux in DMA. The phosphorus yields **27** are readily available from α-bromo ketones **28** by the Arbuzov reaction, followed by treatment with a strong base, such as NaOEt.

15   The reaction of ketones **26** with various amidines **23** [12b-d] (Fig 4) affords, the desired tetra-substituted pyrimidine sub library **a**.

Small sub-libraries b-g having one or more constant functional group on the six member aromatic ring, are characterized by better solubility.
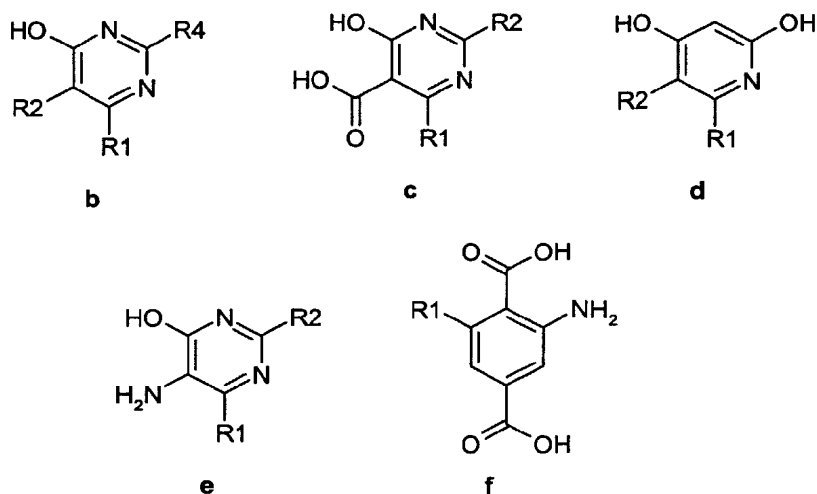
A series of 2,5,6-trisubstituted-4-oxo-dihydropyrimidines **29** can be prepared by SP using a cyclization-cleavage strategy[13] from readily available amidines **23** and resin attached α,β-unsaturated carboxylic acids **30**[14] (see pathway below). Compound **30** is obtained via coupling of the polymer and acyl-chloride **31** (derivetized from commercially available α,β unsaturated carboxylic acids.
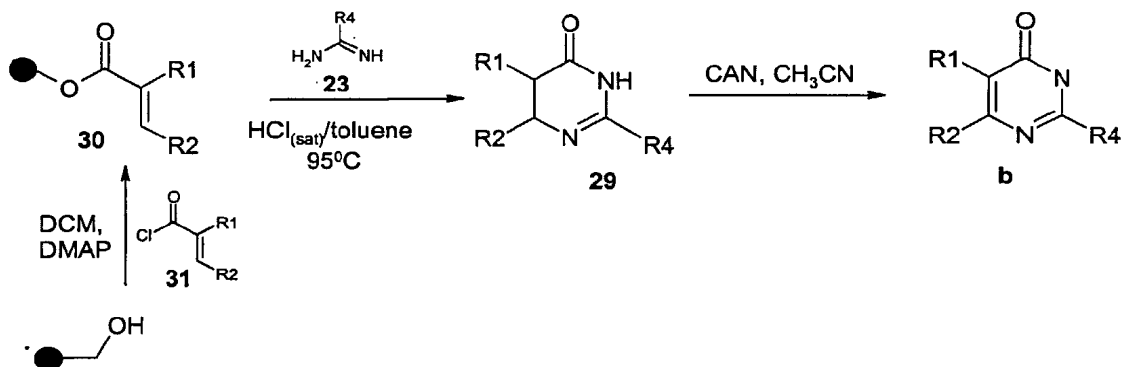
Compounds **29**[13b] can be oxidized (CAN, CH$_3$CN) to corresponding pyrimidines **b**.

A solid phase method for the preparation of Knoevenagel condensation products from resin bound malonates and malonic acids has potential for the preparation of hetero- and carbocyclic compounds. (see pathway below)
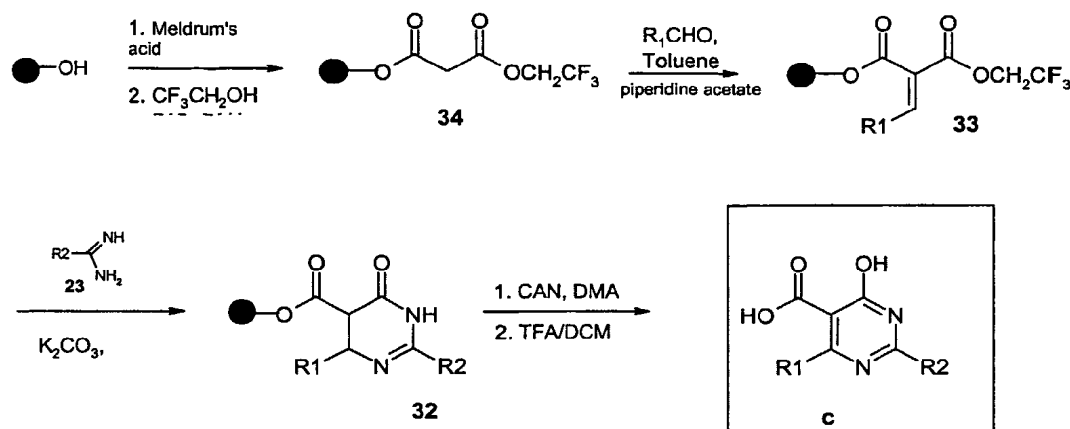
Malonic acid monoester (see pathway above) are prepared from macroporous Wang resin (AgroPore, Argonaut Technologies)[15] by treatment with Meldrum's acids.

Conversion of the unsymmetrical ester 34 was achieved by treatment with trifluoroethanol and DIC, followed by Knoevenagel condensation with the aldehyde in the presence of piperidine acetate to give substituted methylene malonate 33. For the bulk resin preparation of 33 (2-10g of resin), the Knoevenagel condensations are carried out with Dean-Stark trap to eliminate water which gave consistently higher yields and faster reaction). Malonates 33 are treated with 10 equivalents of the amidine hydrochlorides 23 in dimethylacetamide (DMA) solution, with excess K_2CO_3 to neutralize the HCl amidine salt, at 70°C for 4-8h to give resin bound dihydropyrimidones 32 . The reagent consumption progress can be monitored by FTIR observing the adsorptions of C=N and C=O groups. Oxidation of 32 with 0.2M ceric ammonium nitrate (CAN) in DMA[16] affords resin bound hydroxy-pyrimidines. Cleaving under acidic conditions (TFA/DCM, 1:1, RT, 1-2h) gives secondary sub-library c (The sub-library c exists in its tautomeric form- 4-pyrimidone).

The examples for tailor-made synthesis of miscellaneous tetrasubstituted 6-atom membered rings are described below.

The amidines 23-25 react in solution with commercially available [bis(methylthio)methylidene]malononitrile 35 (see pathway below) in the presence of DIEA[17] to give the corresponding methylthiopyrimidines. The latter are oxidized with 1.2 equiv. of m-CPBA in DCM or H_2O_2[18], to form the intermediate sulfinyl derivatives 36 which are subjected to amine substitution with NH_3 [19] (dioxane room temperature)leading, after nitrile hydrolysis

(TFPA)[10], to the final aminopyrimidines **37**. If LiOH is used instead of NH$_3$ the corresponding hydroxypyrimidines **38** [21] after nitrile are obtained.
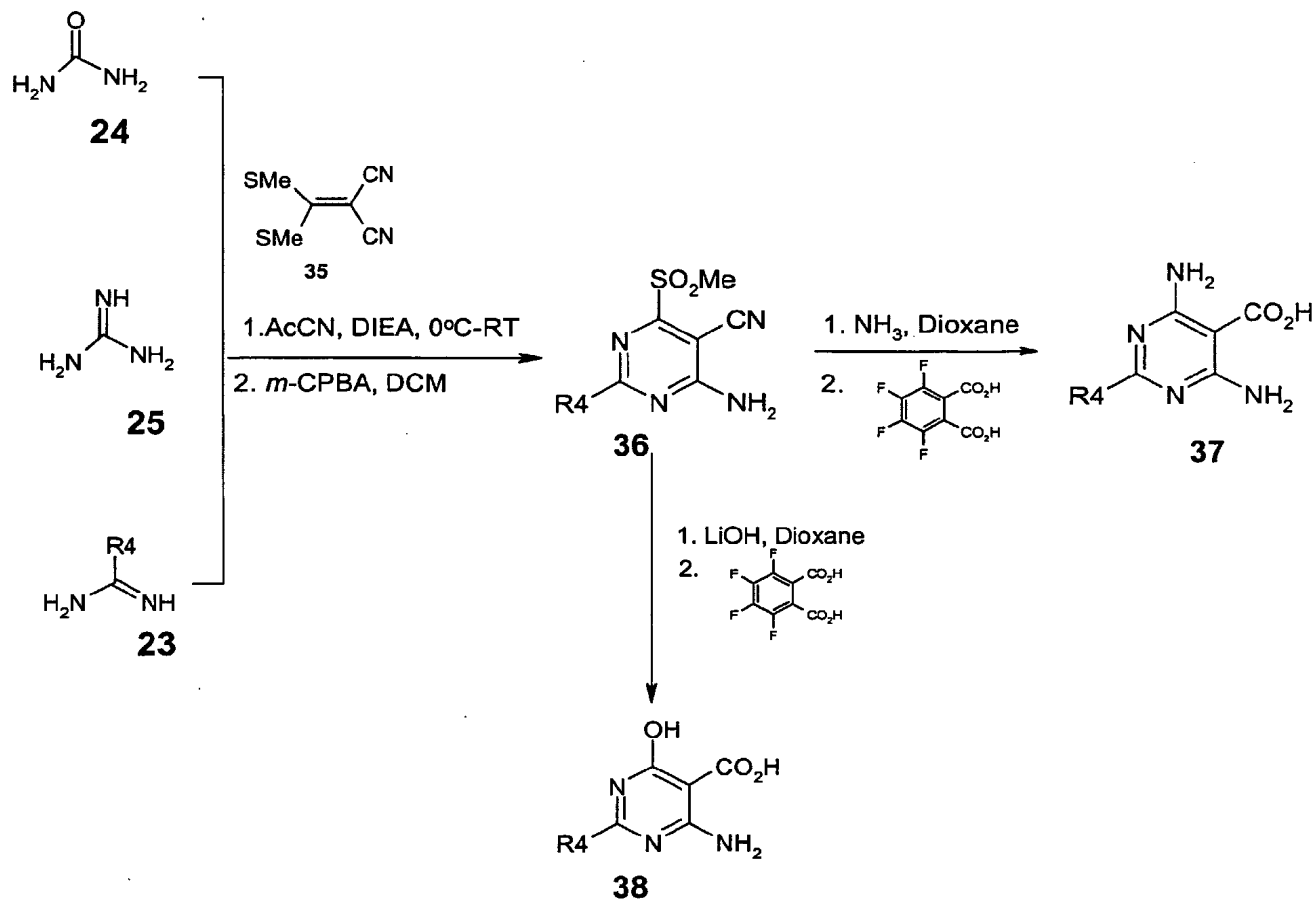
5   A series of various 3,4,5-trisubstituted phenols **39** can be synthesized in high yields using the "cyclization-cleavage " approach [22].
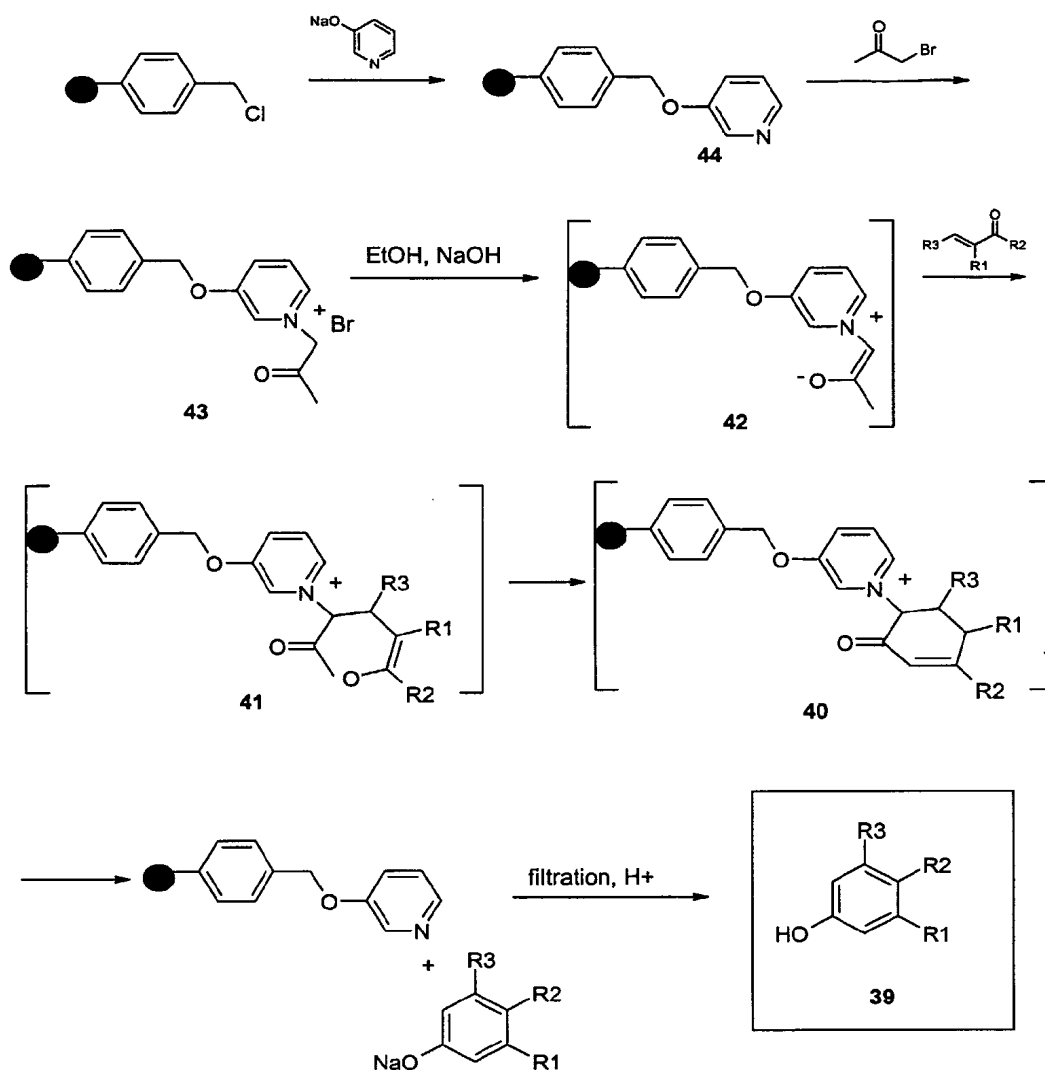
Base catalyzed reactions between α,β-unsaturated ketones and polymer bonded acetonyl groups **42** (see pathway above) result in a tandem Michael addition/annulation reaction with concomitant cleavage from the resin to obtain the desired phenols **39** The synthesis initiates using resin prepared from Merrifield resin by coupling with Sodium 3-hydroxypyridine, producing higher loading capacity resin **44,** which was successfully quarternized by 1-bromopropane-2-one (or 2-bromo 1-phenyl propn-1-one; 2-bromo 1,2 diphenyl ethanone; 2-bromo-1-phenyl butane-1-one; 3-bromo butan-2-one) to afford poly-pyridinium salt **43**.

Reaction of **43** with α,β-unsaturated ketones was carried for 16 h, and after filtration of the resin the library **39** is obtained.

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16.2 Indolo[2,3-b]quinoline 6,6,5,6 cyclic scaffold

The indolo[2,3-b]quinolines **1a,b** synthetic pathway is outlined in the pathway below. The key

5   step in this synthesis is the decomposition of the corresponding triazoles **2a,b** in

polyphosphoric acid (PPA) at 110-160°C, which affords the desired **1a,b** [1,2]. The isomers **2a**

and **2b** can be separated during Purification. The starting triazoles **2a,b** can be prepared by

heating trisubstututed chloroquinolines **3** with benzotriazole building blocks **6a,b** at 110-

120°C in presence of TEA. [1,3]. The benzotriazole building blocks **6a,b** is prepared from

10   monosubstituted nitro-anilines by reduction of NO_2 group ($SnCl_2$ or H_2/Pd) and subsequent

diazotization of readily obtained diamines. [1,4].
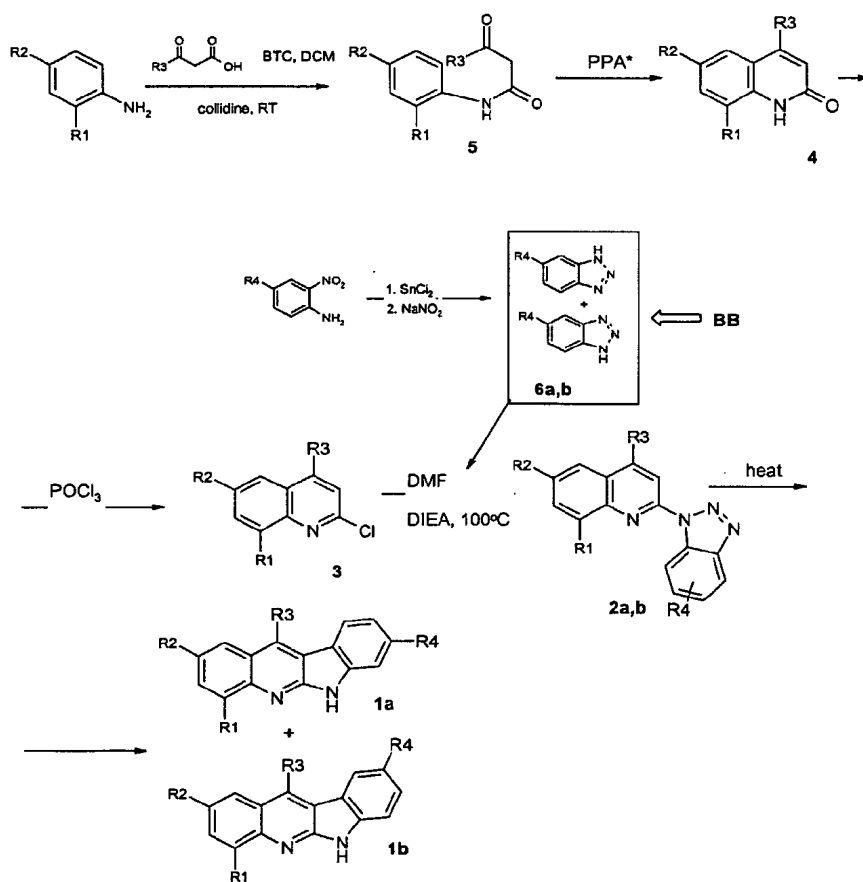
synthesis of Indolo[2,3-b]quinoline

15   2-chloro-quinolines **3** is prepared in three steps from disubstituted anilines first the anilide is

formed either by reaction with preactivated (BTC, DMAP, collidine) β-keto-acids, or with the

free acid at high temperature followed by intramolecular cyclization of **5** under acidic

conditions. Finally the obtained quinolinone is chlorinated with freshly distilled POCl$_3$[5] to afford **3**. Another approach, namely solid-phase synthesis of **1a,b**, can be utilized using disubstituted anilines with solid support attachable functional groups (CO$_2$H, NH$_2$, OH).
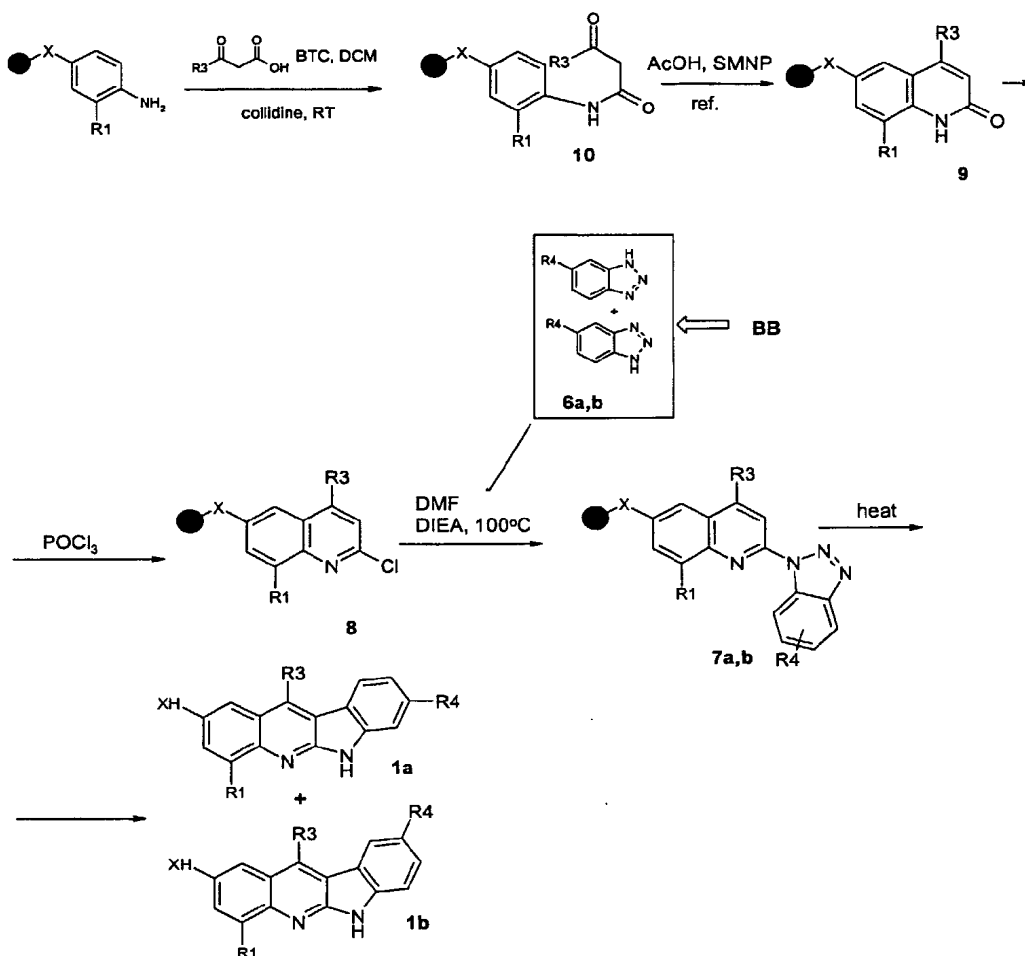
solid phase synthesis of Indolo[2,3-b]quinoline

The starting anilines can be loaded on appropriate resin according to the type of the functional group to be attached. If the functional group is CO$_2$H, the resin will be phenolic (see quinoline chapter change formulation according with the format of the patent) and the loading is performed under esterification conditions (BTC, DMAP); if the functional group is OH, the loading can be performed by Mitsunobu reaction; and if the functional group is NH$_2$ the starting aniline will be loaded under sulfonation conditions on sulfonyl chloride resin or alternatively prepared by Curtius rearrangement from corresponding carboxyl derivatives.

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4. Org Syn Col Vol 1 3 106

5. Org Syn Col Vol 3 194

6. for other synthetic method for the preparation of Indolo[2,3-b]quinoline see

   a. from acylbenzotriazole and acyl isocyante, J Org Chem 65 8069 2000

   b. coupling of 3-bromoquinoline with 2-amino boronate, Synlett 1067 1997

   c. via a modified Graebe Ulmann reaction, J. Med Chem 37 3503 1994

16.3 isoindoloindoles and isoindoloindolones 6,5,5,6 tetra cyclic scaffolds

Herein, is described the Pd catalyzed annulation[1] to form an isoindoloindole skeleton from

5 readily prepared imines and internal aryl acetylenes.

Imines and disubstituted acetylenes undergo a multistep reaction in the presence of palladium

catalyst to produce isoindoloindoles[2], which are obtained in good yields (see pathway below).
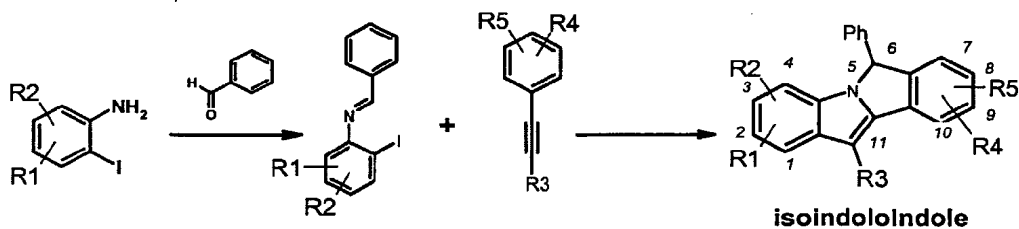
general scheme for the preparation of isoindoloindoles

10

By using divers building blocks – either mono- or di-substituted iodo-anilines 7, and premade

di- or trisubstituted phenyl acetylenes 5.

A large library of isoindoloindols1-4 can be obtained (see pathway below).

15
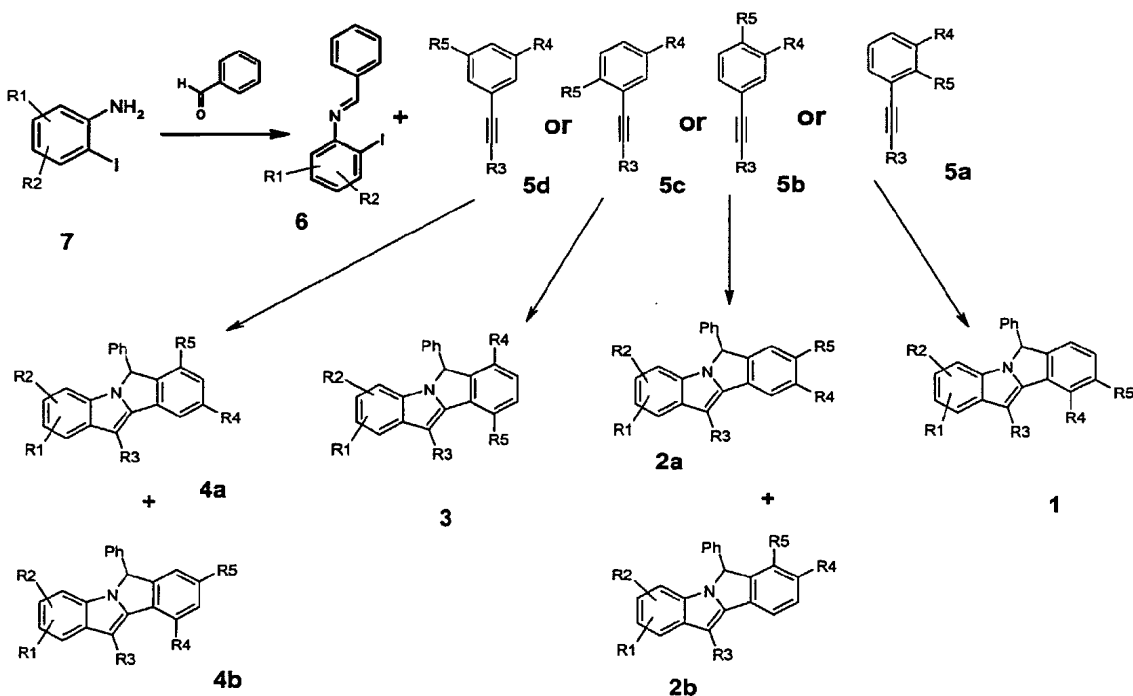
This annulation reaction comprise of two steps synthesis without isolation of intermediate

iodoimines 6. The steps of the synthesis are as follows:

116

1. Imine **6** is formed in solution using drying reagents such as TMOF, molecular sieves or Na$_2$SO$_4$.

2. The acetylenes **5** are prepared by Heck reaction between commercially available or pre-formed di- and monosubstituted iodobenzenes and monosubstituted acetylenes using standard Pd catalysts [3-8] (see pathway below). Modified Heck reaction on solid phase can also be used [9-12]. When we use solution phase, the reaction mixture can be used for the next step as it, without recovering the catalyst, because the one is required for the next step.
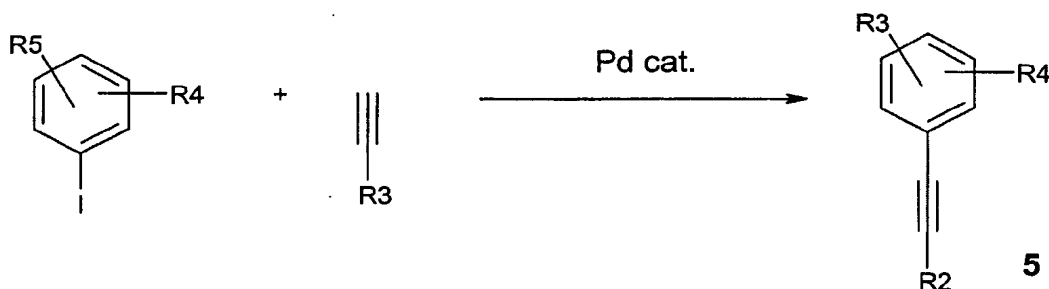
Heck reaction for the preparation of substituted phenyl acetylenes

3. The annulation of internal alkynes to isoindoloindoles using Pd(OAc)$_2$ in the presence of an amine LiCl or Bu$_4$NCl in DMF.

When one of the substituents is at *ortho-* position, the ring closure will proceed in regioselective manner affording single tetra-substituted isondoloindoles **1,3**.

When *ortho-* position on **5** is unoccupied, some substituents control regioselectivity of ring closure by chelating the palladium in the σ-palladium intermediate, which is formed during the reaction. Other cases the two isomers can be separated by chromatography.

For generation of 11-hydroxy isoindoloindoles: TMS protected hydroxyalkyne **11** can be utilized, generating after TMS removal (*n*-Bu$_4$NF) 11-hydroxy-isoindoloindole sub-library **12** (see pathway below).
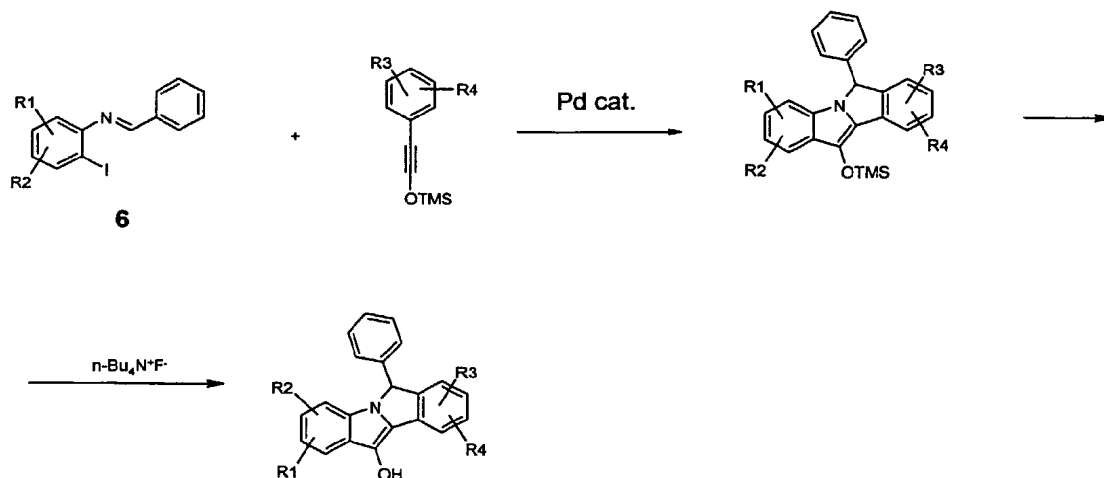
For generation of 11-amino-isoindoloindoles, carboxyalkyne **5** can be used for preparation of
11-carboxy-isoindoloindoles **1-4**. The last can be converted to corresponding azodocarbonyl

5   **14** (*n*-BuOCOCl, then NaN$_3$)[13-15] (see pathway below), which can undergo rearrangement
through nitrene intermediate to provide desired 11-amino-isoindoloindole sub-library **13**.
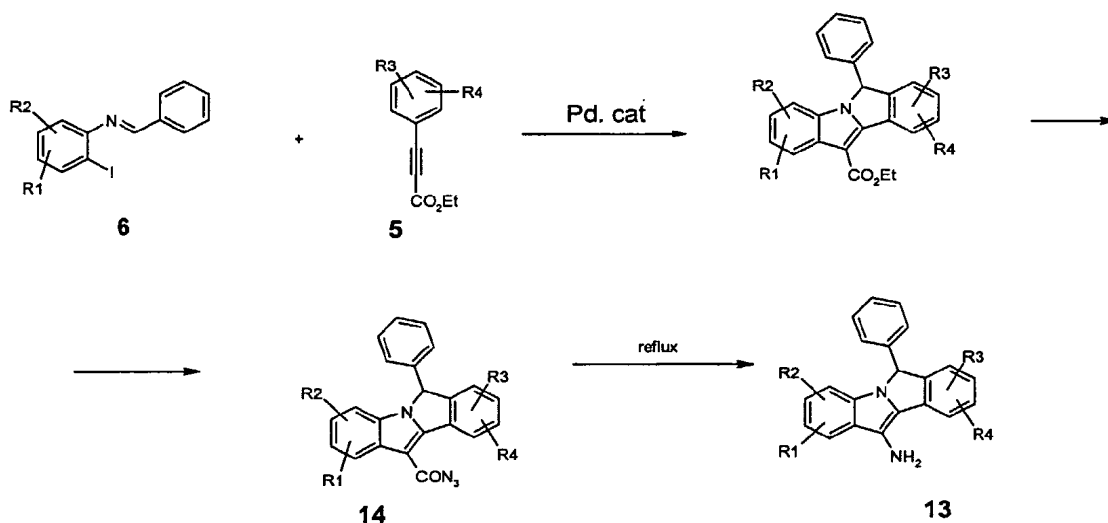
Constant polar functional group can be added such as guanidine. The most convenient location

10   for this purpose is the *para* position on phenyl ring derived from imine **10** (see pathway
below). The imine **10** bears Bpoc protected amine group, which can readily be deprotected,
after annulation with appropriate alkyne, to give **9**. Amino isoindoloindole **9** can react with
bis-Boc thiourea[16] (HgCl$_2$, TEA) to obtain, after subsequent deprotection (TFA/DCM), the
final library **8**.
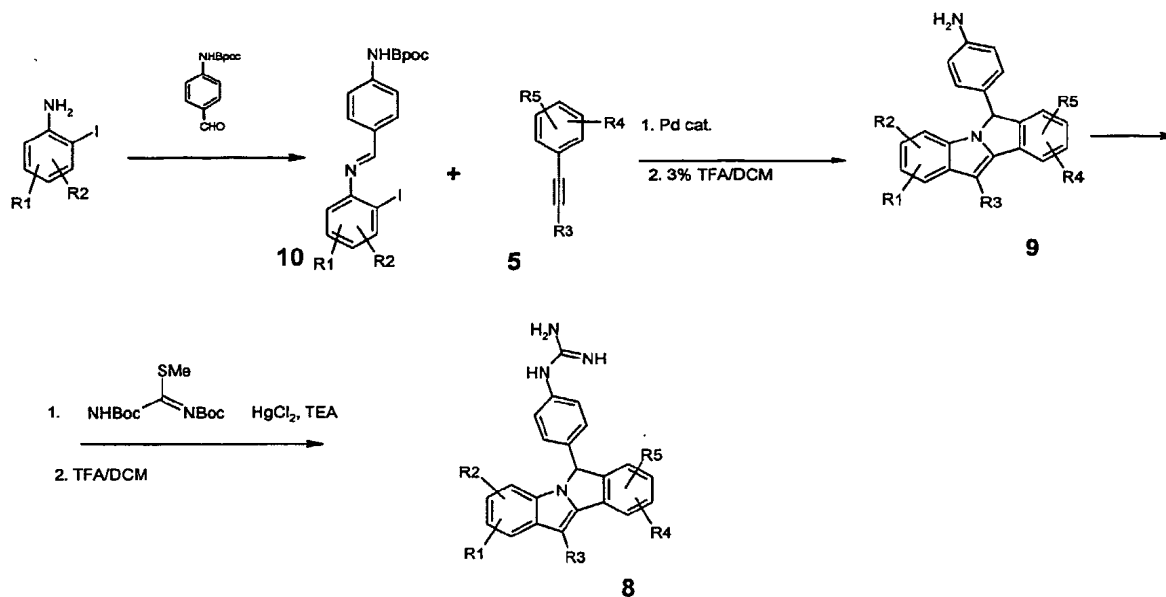
16.3.1 Isoindoloindolones

A slightly modified isoindoloindolone scaffold (see below) can be prepared by two systematic

5   routes:
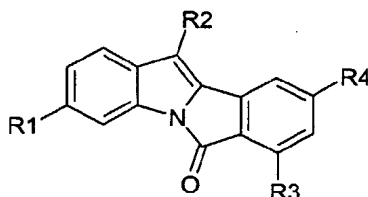
A schematic description is shown in the pathway below:

The approach presented above is divided to three major steps:

1. Formation of di- or tri-substituted indoles: via – Heck reaction between an acetylene

10   and iodoaniline

2. Benzoylation of indole ring with *ortho*-iodo-benzoyl moiety. The coupling of

disubstituted *ortho*-iodo benzoic acid BB to indole 18 can be carried out in to ways: 1.

Regular coupling of BB to indole using DCC/DMAP[17]; 2. Using a pre formed acid

chloride[18, 19].

18

17

15
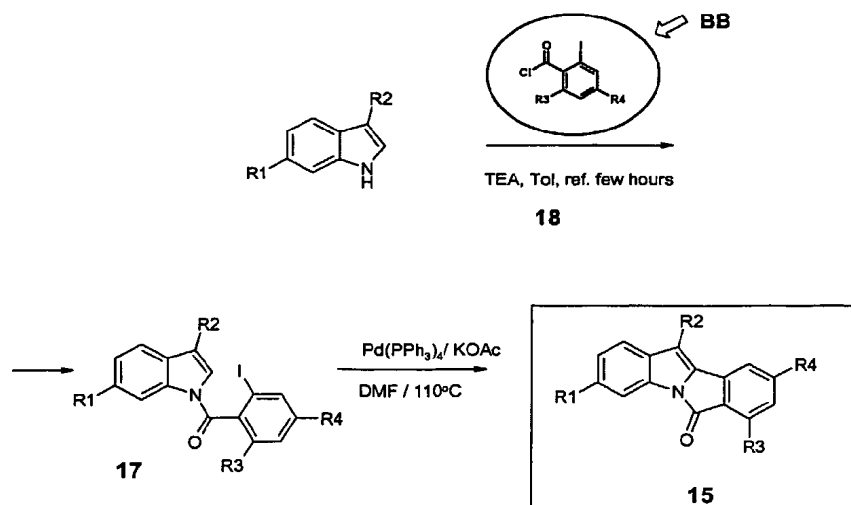
3. Cyclization using Pd catalyzed reaction (Heck annulation)[20, 21]. The addition is very specific using iodo-benzoyl ring. In case the 7th position is not occupied it can add to 7 position of the indole instead of position 2. This addition gives us a new scaffold, which is another library (see pathway below).
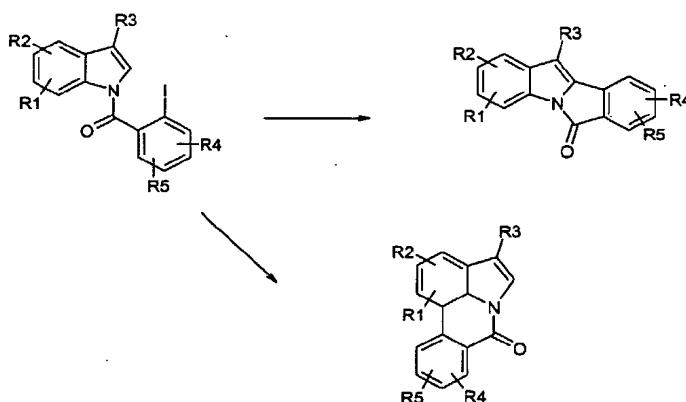
The indole **18** can be prepared by traceless solid phase indole synthesis using indole N-H as a resin attachment point [22], which could be cleaved to give the free indole **18**. One of the most efficient solution phase methods of indole synthesis is the Pd(0)-mediated reaction of 2-iodo-anilines with acetylenes in the presence of base as developed by Larock [23,24].

Monosubstituted 2-Iodoaniline, after loading onto the THP resin through an aminal linkage using PPTS can give **20** (see pathway below). Replacing the catalyst to Pd(PPh$_3$)$_2$Cl$_2$ and using the DCE soluble base TGM, were found to be beneficial in pushing the annulation reaction to completion, affording **19**. Resin cleavage with 10% TFA then can give the free indole **18**. It

was found that TMS-substituted acetylenes readily went to completion at 80°C with almost complete regiocelectivity.

The carboxylated **15** (R_2 = CO_2H) can be converted to amine analog **16** through the corresponding azodocarbonyl, which can undergo rearrangement through nitrene intermediate to provide desired amino-isoindoloindolone sub-library.
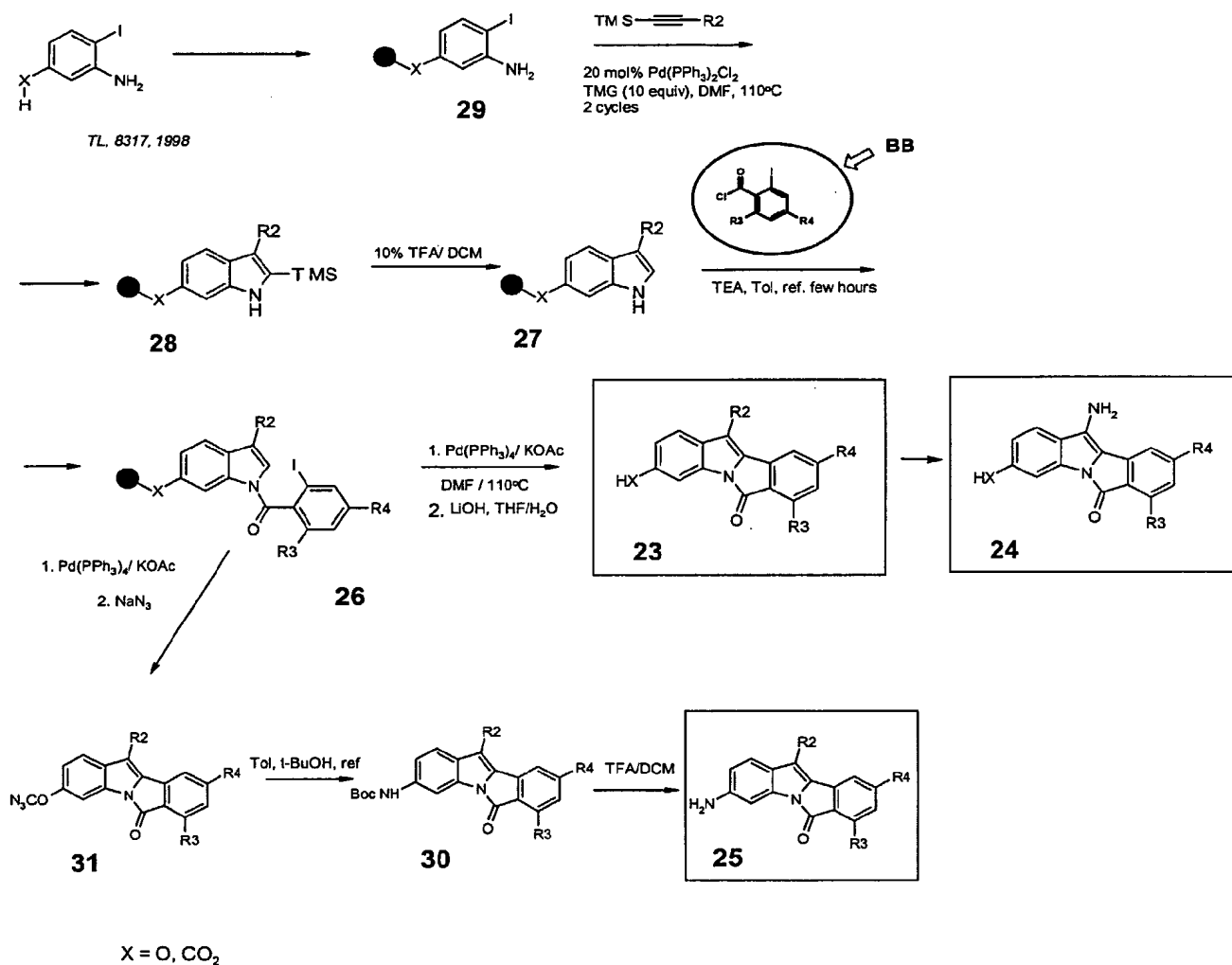
preparation of isoindoloindolone

The hydroxy- and carboxy isoindolones **23** (X = O, CO_2) can be generated by SP synthesis (see pathway above) starting by loading the appropriate iodo-aniline on the resin [9] and effecting the annulation with TMS acetylenes.

The subsequent benzoylation and annulation of **27** followed by cleavage from the resin affords **25**.

A second way of formation of isoindoloindolones presented in the following pathway[25]:
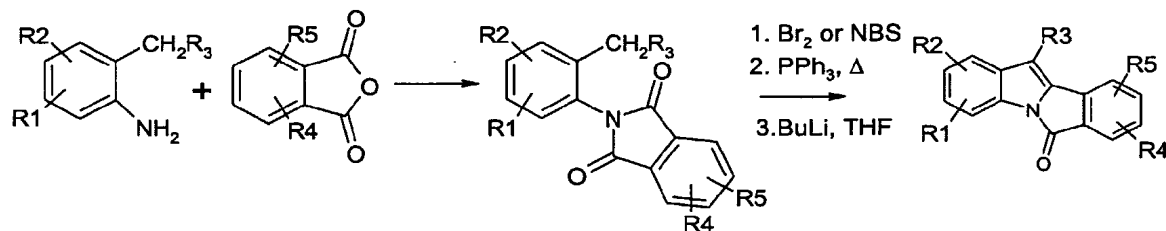
A key step is an intramolecular wittig reaction. Substituted *ortho*-alkyl anilines and phthalic anhydride derivatives react to form aryl phthalimides. These can be converted to phosphonium salts and can be closed to isoindoloindolone system.

References:

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5

16.4 The single atom scaffold

The smallest scaffold used in this implementation is the single atom scaffold, namely one
carbon scaffold, of the general structure **a**:

R1\
R4—C—R2\
R3

a
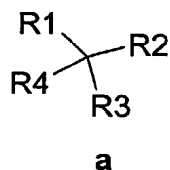
The library **a** consists of several sub-libraries **b-e** (see below) that represent compounds with
one constant functional group and independent variety of substituents around the carbon:

R1\
HO—C—R2\
R3

b

R1\
H$_2$N—C—R2\
R3

c

R1\
HO$_2$C—C—R2\
R3

d

O‖\
R1—C—R2

e
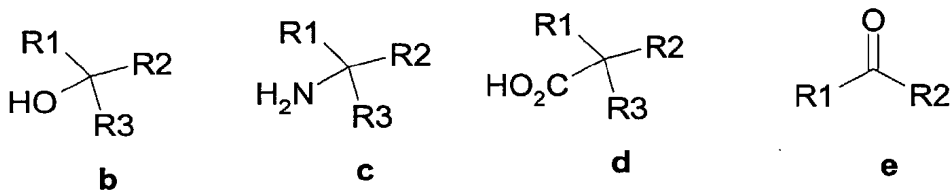
The secondary sub-libraries comprising two or three constant polar functionalities (see below)
may be somewhat limited, because of the chemical unstability of molecules bearing two or
three geminal amines or hydroxyl atoms (compounds **f-j**):

R1\
HO—C—R2\
OH

f

R1\
H$_2$N—C—R2\
OH

g

R1\
H$_2$N—C—R2\
NH$_2$

h

O‖\
H$_2$N—C—OH

i

O‖\
HO—C—OH

j
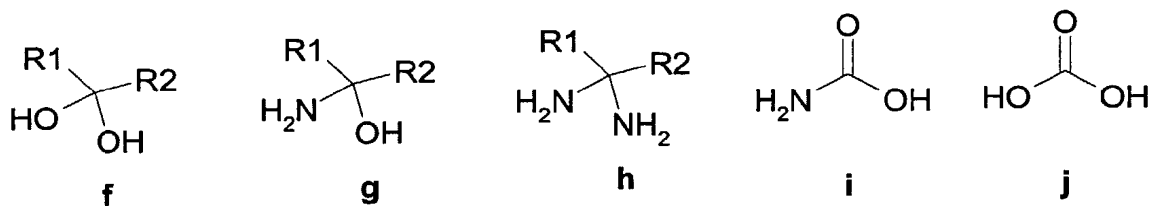
However, the synthesis of the α-amino acids **k**, α-hydroxy acids **m** and α-dicarboxylic l acids
are known. For example they are described in: Synthesis of optically active α-amino acids by
Robert M. Williams, Pergamon Press.

Some of the compounds based on the carbon scaffold are mostly commercially available. Those that are not commercially available can be synthesized, mostly in solution, by conventional methods.

The tetriary alcohols **b**[1] can be synthesized through the well known epoxidation of olefins 2(as a

5   key step, producing epoxides 1, which already possess the required substituents[2] (see pathway below)
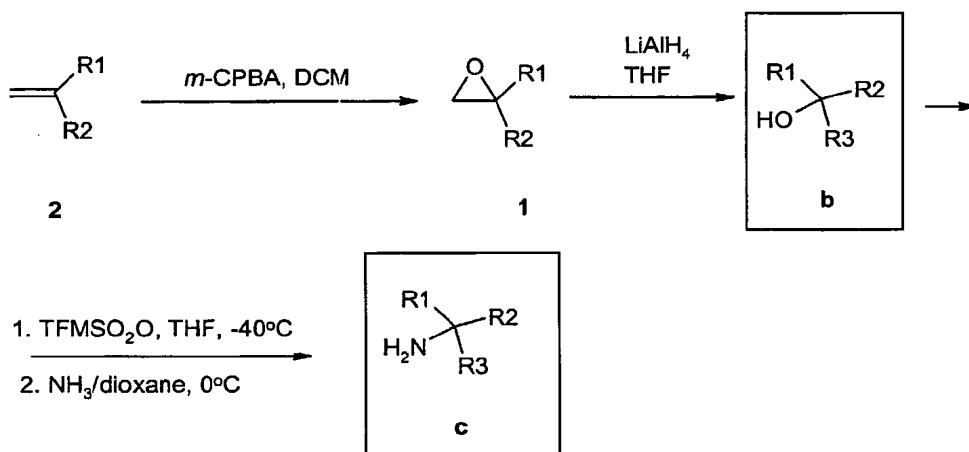
Electron-donating groups typically increase the rate. Conditions are mild and yields are high.

10 The consequent reduction of epoxides is easily carried out. The most common reagent is LiAlH$_4$, which reacts through the inversion of configuration 2[3]. As expected from the SN2 mechanism, cleavage usually occurs so that the desired tertiary alcohol **b** is formed. Product **b** serves as the starting material for the tertiary amines **c**, which are obtained from **b** by substitution of corresponding trifluoromethylsulfonate with ammonia in dioxane.

15 The solid phase preparation of the tertiary alcohols **b** has been recently reported[4]. Actually, this new cleavage strategy involves addition of carbon nucleophiles to ester bound polymers 3.
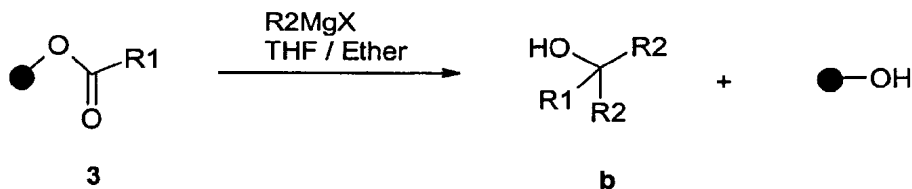
By this mode can be prepared only tetriary alcohols with two identical alkyl or phenyl substituents (R2), thus, limiting the diversity of the products, but still able to generate rapidly the secondary sub-library of the tetriary alcohols.

The α-hydroxy acids **m** can be obtained by straightforward one-pot procedure from the corresponding α-keto acids **4** (pathway below). α oxo acid **4** are commercially available and their treatment with Grigniard reagents (2 equiv., THF, -40°C-RT) lead to the desired **m** products.
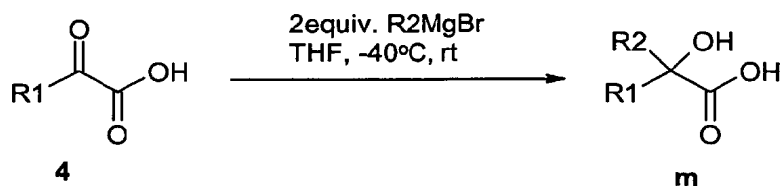
A Schiff base activated glycine supported on a soluble polymer (PEG) **6** can be readily alkylated with the wide variety of electrophiles in the presence of carbonate base (Cs$_2$CO$_3$) in acetonitrile[5] providing non-stereospecific amino acid esters.

Similarly, Schiff base activated amino acids *t*-Butyl esters **8** can be alkylated to α-C disubstituted analogs **7** (pathway below) using alkyl bromides and the LDA as a base (LDA, THF, -40°C).
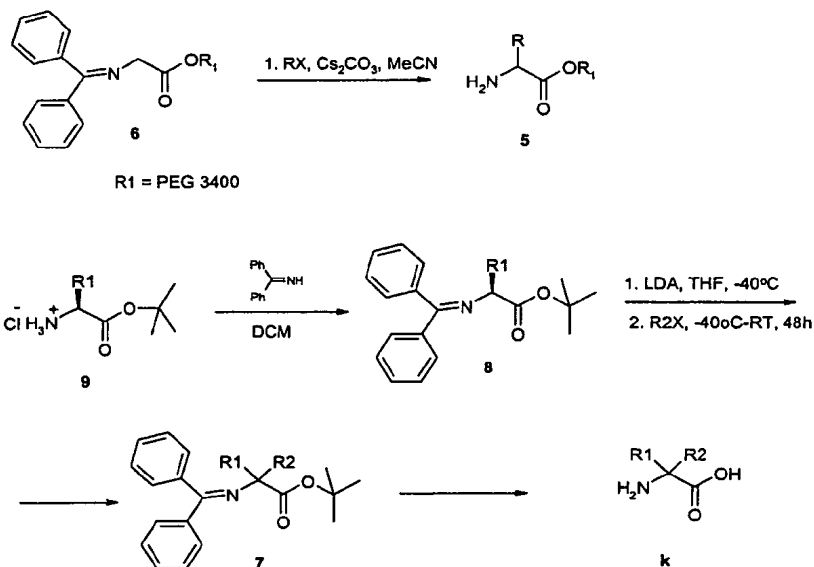
The Schiff bases **8** can be prepared by transimination of the commercially available *t*-Bu ester of amino acids **9** with benzophenone imine. Finally, The alkylated product can be totally deprotected by TFA/DCM yielding the desired secondary sub-library **k**.

It should be mentioned that all products generated in this chapter are enantio-unselective and require separation of enantiomers on chiral column. The utilization of racemic mixtures could be also considered

References:

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2.   *Russ. Chem. Rew.*,986, (1985).

3.   *J. Org. Chem.*, 52, 14, (1981).

4.   S. Chandrasekhar, *J. Comb. Chem.*, **2**, 246, (2000).

5.   a. B. Sauvagnat, *Tet. Lett.*, **39**, 821, (1998).;

            b. B. Sauvagnat, *J. Comb. Chem.*, **2**, 134, (2000).

16.5 Benzodiazepines 6,7 bicyclic scaffold

Benzodiazepines are therapeutic and anticonvulsant agents. As such the 1,4 benzodiazepines

5   have been the target of several solid phase synthetic strategies.

The synthesis of 1,4-benzodiazepines, is based on the closure of a seven membered ring, via

lactamization in high yield. [1-8]

A slightly modified solid phase approach, which is based on the ring closure, via an imine

moiety is described in the pathway below.

10
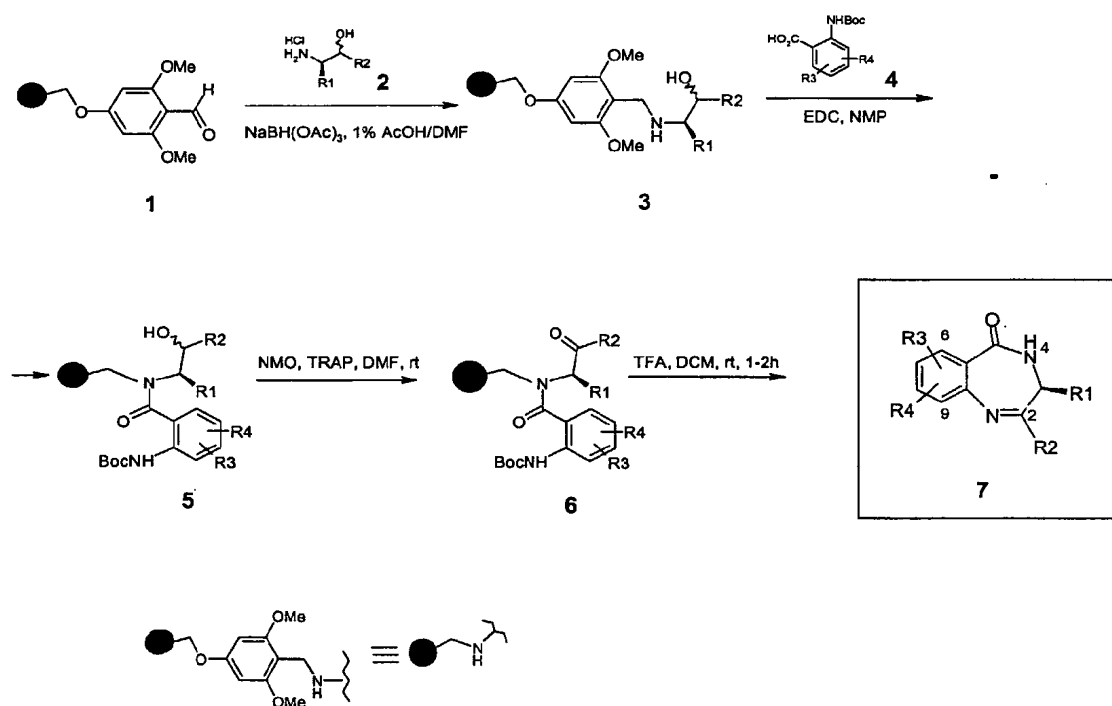
Solid phase synthesis of benzodiazepines

According to this strategy the aldehyde resin 1 [3] is coupled to β-amino-alcohol 2 via reductive

15   alkylation (Fig 1). β-aminoalcohol (2) can be prepared in two alternative routes (see pathway

below):

    (1) Coupling of N-methoxyhydroxamate (8) with Griniard reagents (R_2MgBr) to obtain

        the corresponding ketones, followed by reduction using $NaBH_4$ (MeOH, rt, few hours)

to afford the Boc protected amino-alcohol derivative (9). Removal of the protecting group yield 2.

(2) Reducing N-methoxyhydroxamate (8) with LiAlH₄ to the aldehyde derivative followed by coupling with Grinard reagents (R₂MgBr) to form the Boc protected amino-alcohol derivative (9). Removal of the protecting group yield 2.
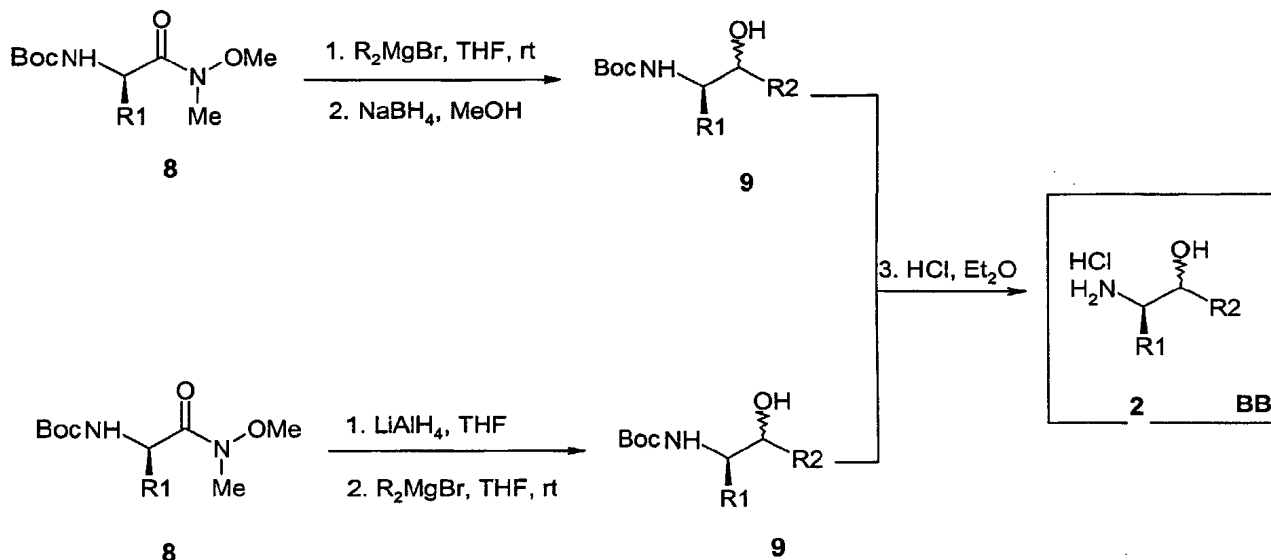
Synthesis of β-aminoalcohol

The coupling between the aldehyde resin (1) and the amino-alcohol hydrochloride salt (2) is done via reductive alkylation using NaBH(OAc)₃, 1% AcOH, DMF to give the resin immobilized β-amino-alcohols 3. To avoid racemization, it is desirable to obtain equilibrium between the resin bound aldehyde 1 and β-amino-alcohols 2 before addition of the reducing agent to the reaction mixture.

Coupling between the secondary amine 3 and Boc protected disubstituted anthranilic acids 4 leads to resin bound intermediate 5. Oxidation of the hydroxy group to affords 6. The oxidation on solid support can be carried out by Py.SO₃ [9] complex in DMSO at room temperature, or by the alternative procedure using NMO [10] (N-methylmorpholine N-oxide) with TPAP (tetra-n-propylammoniumperruthenate) catalyst, in DMF at room temperature. Compound 6 is deprotected (TFA/DCM), and the free amine undergoes intramolecular cyclization under acidic conditions to obtain the desired benzodiazepine 7.

Introduction of amine or hydroxyl at position 3 of 1,4 benzodiazepines will result in decomposition of the material. At position 2, an OH group will isomerise to the keto form, while an NH_2 group can form tautomers with the imine group.

The synthesic route for the preparation of a benzodiazepine having an NH_2 substituent at position 2 is described in the two pathways below:

(1) Thioamino ester (10) is loaded onto aldehyde resin 1 by reductive alkylation $(NaBH(OAc)_3, 1\%$ AcOH in DMF) to obtain resin bound intermediate 11 (Fig 3). The secondary amines (11) is coupled with disubstituted anthranilic acids (12) (EDC, NMP) to form amide 13, which can undergo the intramolecular cyclization using lithiated p-methoxy acetanilide (14)[1] to give thiobenzdiazepine 15. The cyclic resin bound thiointermediate 15 is submitted to methylation (MeI) followed by oxidation to generate preferable leaving group (namely methylsulfoxide) for nucleophylic substitution. Such substitution reactions can be operated with acid labile dimethoxy benzylamine under standard conditions (16)(DMF, DIEA) providing after acidic cleavage the desired 2-amine benzodiazepine sub-library 17.

(2) An alternative synthesis of 2-aminobenzodiazepine is as follows, Benzodiazepine 2,5 dione (20) is formed by coupling of substituted anthranilic acid with amino-acid followed by ring closure, which reacts with Lawesson reagent to form intermediate-2-thiobenzodiazepine-5 one (21). The amine 22 is obtained by reaction between the benzodiazepinethione 21 and ammonia.

synthesis of 2-aminobenzodiazepine
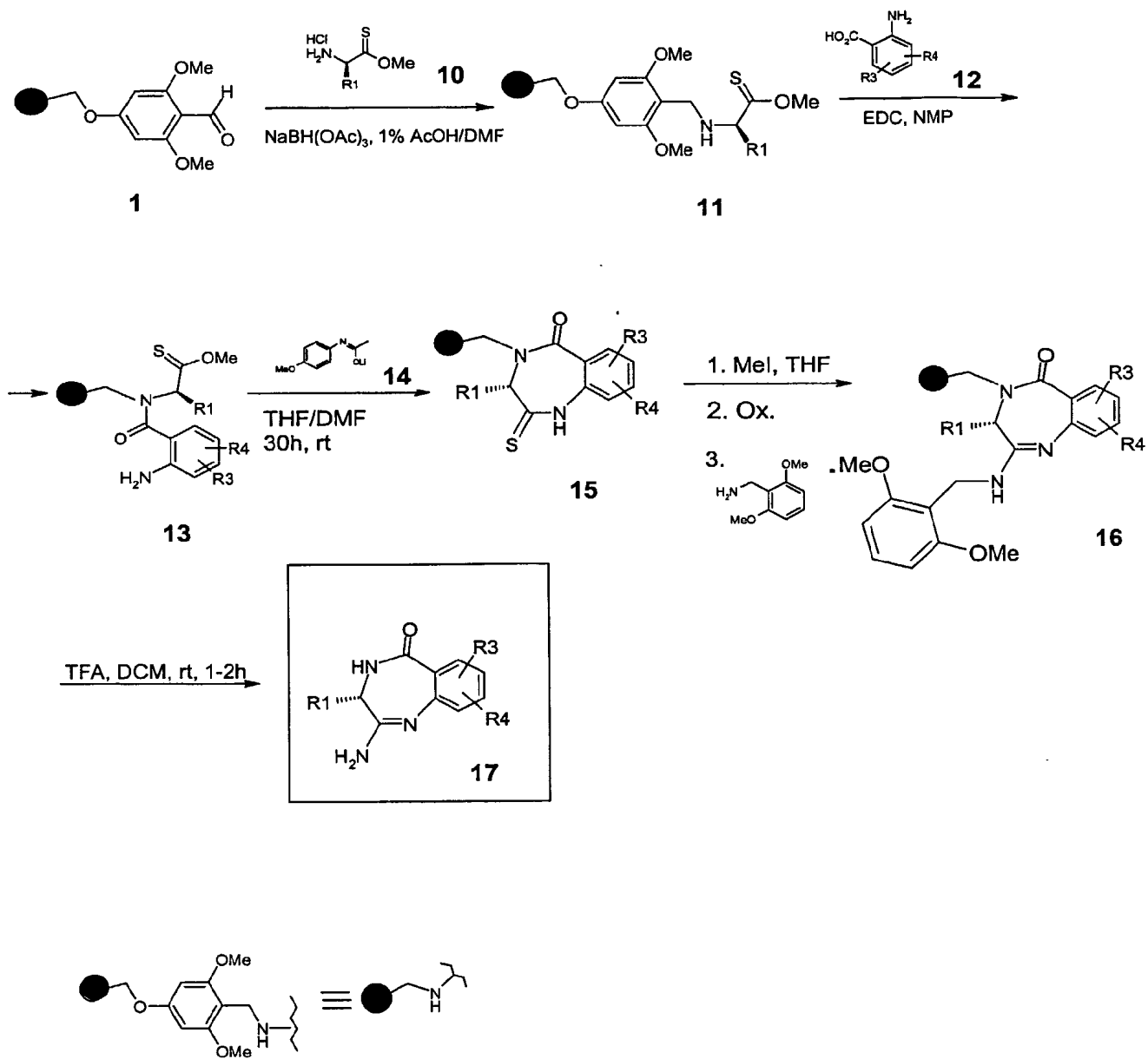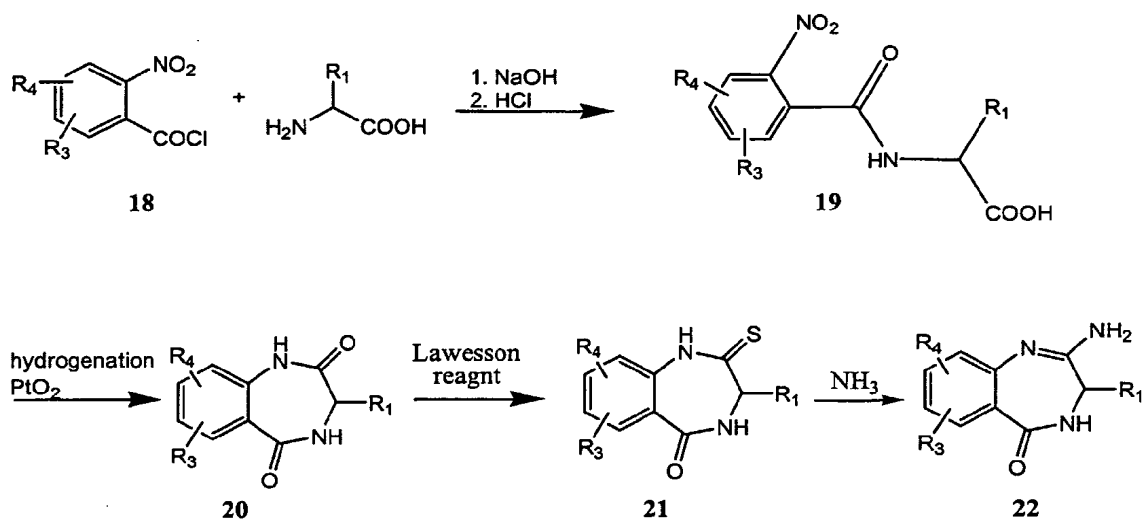
alternative synthesis of 2-aminobenzodiazepine

The synthesis of β-hydroxy α amino- acid, a building block used for the preparation of 2-

5   carboxy benzodiazepine is described in the following pathway. Commercially available chiral

Fmoc serine t-butyl ester **26**, undergoes Sworn oxidation ($(COCl)_2$, DMSO) to obtain the

aldehyde **27**. The aldehyde **27** is subjected to Gringard reaction R1MgX to form the Fmoc

protected amino-alcohols, which after Fmoc removal (piperidine, MeOH) leads to desired

building blocks **28**. In case when both R_1 and R_2 are carboxyl groups, the starting material is

10   di- *t* Butyl fumarate **23**, which upon epoxidation (mCPBA, $NaHCO_3$, DCM) gives the epoxide

24, followed by ammonia in methanol to afford **25**.
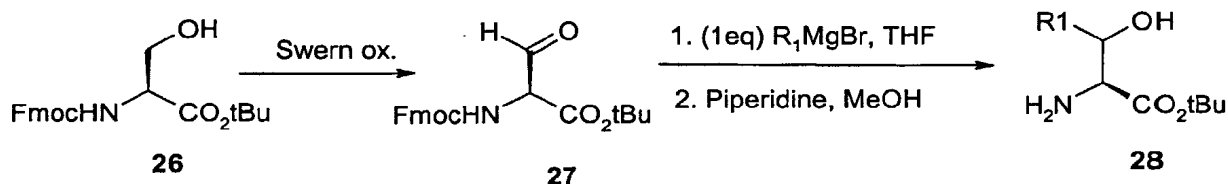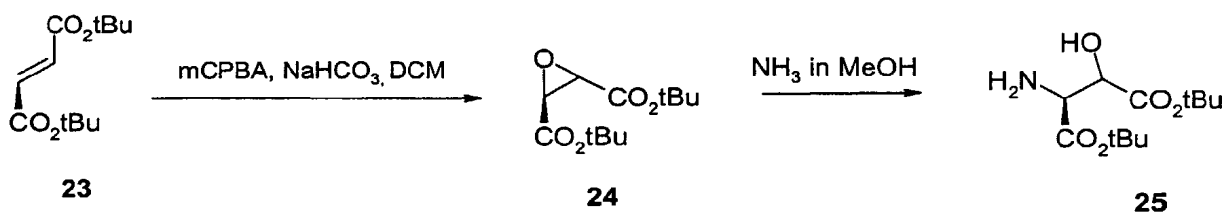
Preparation of b-hydroxy amino acid

The synthesis of benzopyridodiazepine[11,12] **33** is described in the pathway below. 2-chloro-3-aminopyridines **29**[12] is coupled with disubstituted azidobenzoyl chloride building block **30**. Reduction of the azide **31** with SnCl$_2$ provides the 2-chlorooxazolidine intermediate **32**, which upon treatment with acid rearranges to the desired pyridine-based tricyclic scaffold **33**.
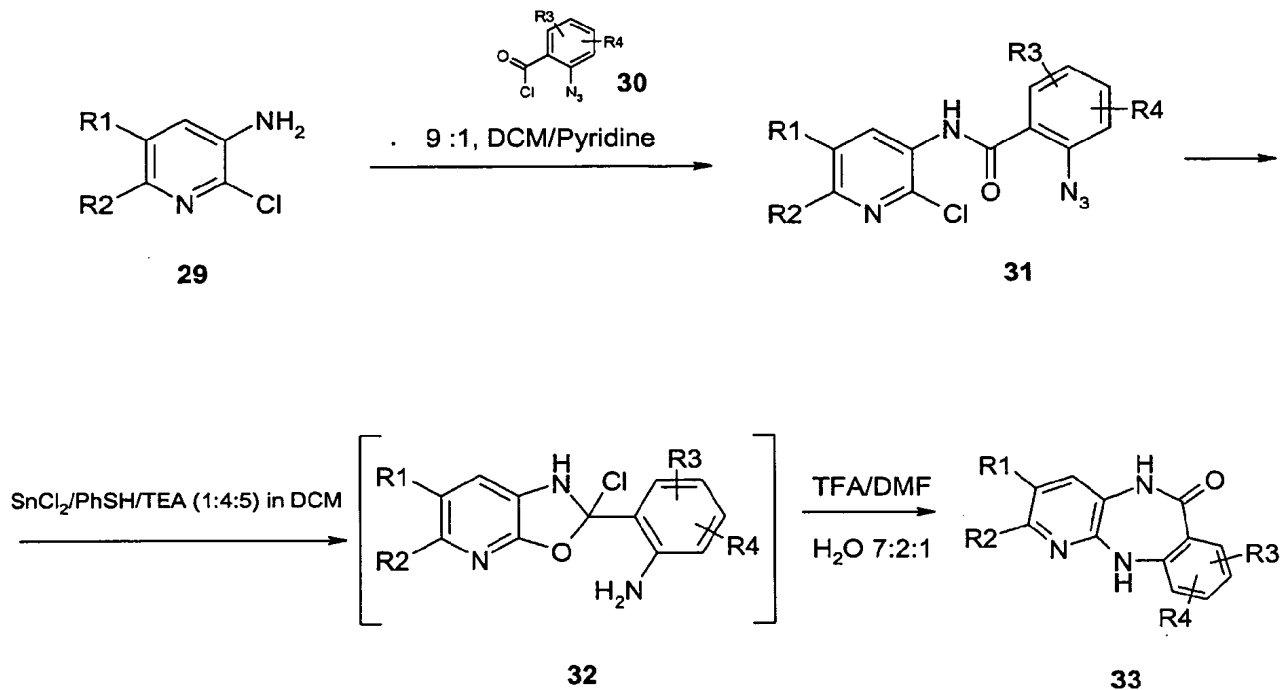
preparation of benzopyridodiazepine

The synthesis of the oxy analog of **33** namely 10*H*-Dibenzo[*b,f*][1,4]oxazepin-11-one is described in the pathway below. Disubstituted *O*-aminophenol building unit **35** is attached to the resin on the Acid sensitive MEthoxy BenzAldehyde **(AMEBA)(34)** via reductive amination, to form **36**.

Resin **36** was further modified with monosubstitued 2-fluoro-5-nitrobenzoic acid **37** using HOAt/DIC strategy to afford immobilized substrate **38**, which was ready for the assembly of the nitro-10*H* dibenz[*b,f*][1,4]oxazepin-11-one analogs **39** (The key cyclization step (S$_N$Ar) between the fluor and the phenolic oxygen was performed using a 5% DBU in DMF[23, 24, 25]). The reduction of the nitro group in the resulting resin can be obtained with the 1.5 M solution of SnCl$_2$ H$_2$O in DMF, and subsequent cleavage (TFA/DCM) from the resin 2-amino sub-library **39** is obtained.

38
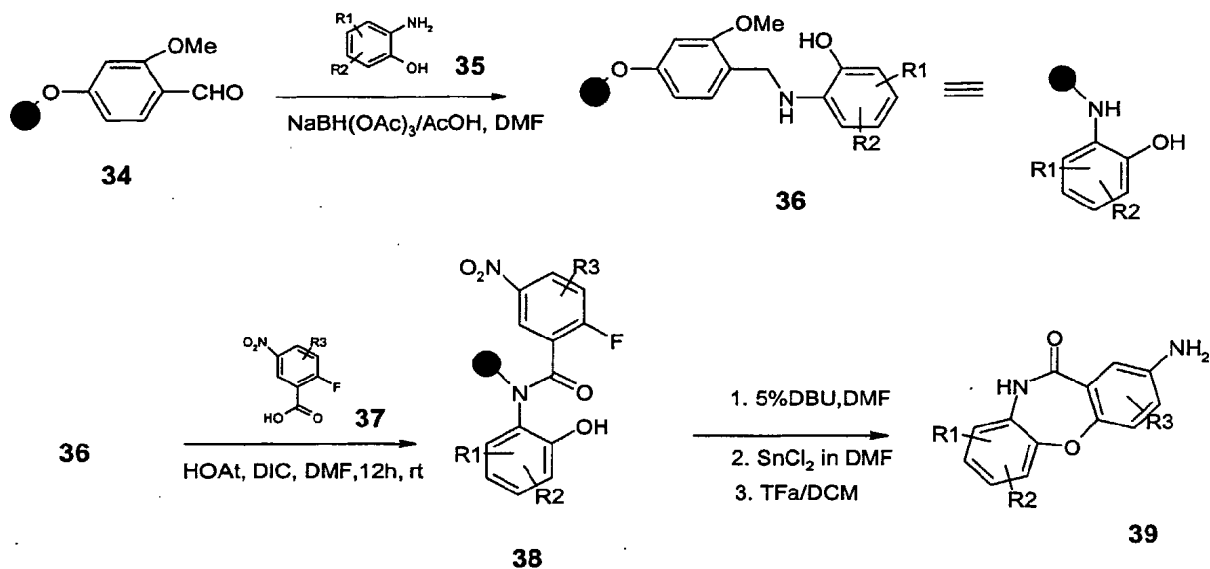
Synthesis of dibenzo-oxazepinone

References:

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12. J. Org. Chem, 62, 6102,1997.

13. Tet, 55, 2827,1999;

14. Tet , 55, 8295,1999;

15. Tet. Lett, 40, 5827,1999

16.6 Pyrazinoquinazolinone -6,6,6 tricyclic scaffold

1
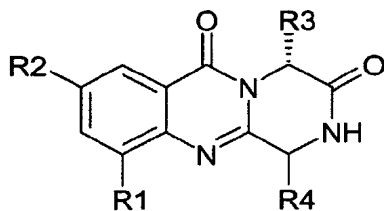
The pyrazino[2,1-b]quinazoline-3,6-dione system can be considered as a constrained peptidomometic and is present in several families of natural products . Some of these compounds exhibit very interesting biological activity (J. Antibiotics 46, 380, 1996, Annu Rev Biochem 62 385, 1993).

One currently known syntheses of this scaffold can be grouped as follows:

a: Transformation of 4-substituted 2,5-piperazinediones into the corresponding iminoethers followed by cyclocondensation with anthranilic acid or methyl anthranilate. [1-5]
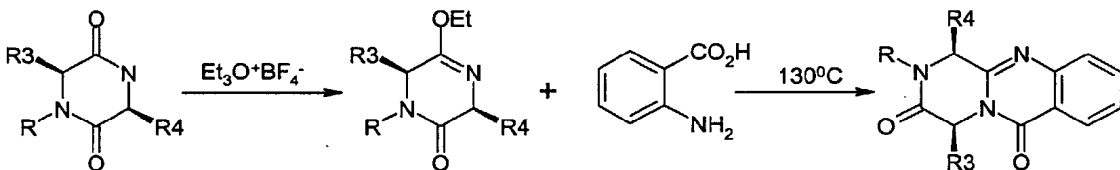
iminoether anthranilic acid condensation to Pyrazinoquinazolinone

b: Acylation of 4-substituted 2,5-piperazinedione with o-azidobenzoyl chloride followed by Staudinger reaction with phosphine to yield the corresponding γ-phosphazene and subsequent intramolecular aza wittig cyclization of the latter imtermediate. [6,7]
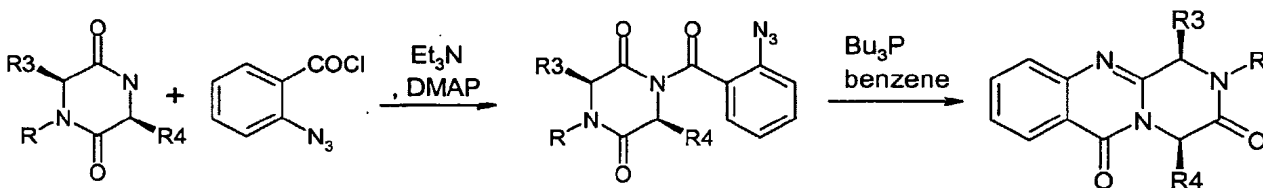
Pyrazinoquinazolinone via N-o-azidobenzoyl-diketopiperazine

In a modified reaction sequence the N-o-azidobenzoyl-diketopiperazine is formed via an open chain tripeptide where the anthranilic acid unit is the N terminal unit bears an azido group as masked amino function[8]. Cyclization generates the quinazolinone ring.

c: Double cyclization of an open chain tripeptide via 4-imino-4-H-3,1-benzoxazine intermediate prepared through cyclodehydration of a suitable o-acylanthranilamide in the presence of iodine triphenyl phosphine.

This method was reported in solution [9-13] as well as on solid phase [14], which makes it a good mean for parralel array synthesis therefore suitable for our purpose.

EDC 1-ethyl-3(3-dimethylamino)-propyl)carbodiimide
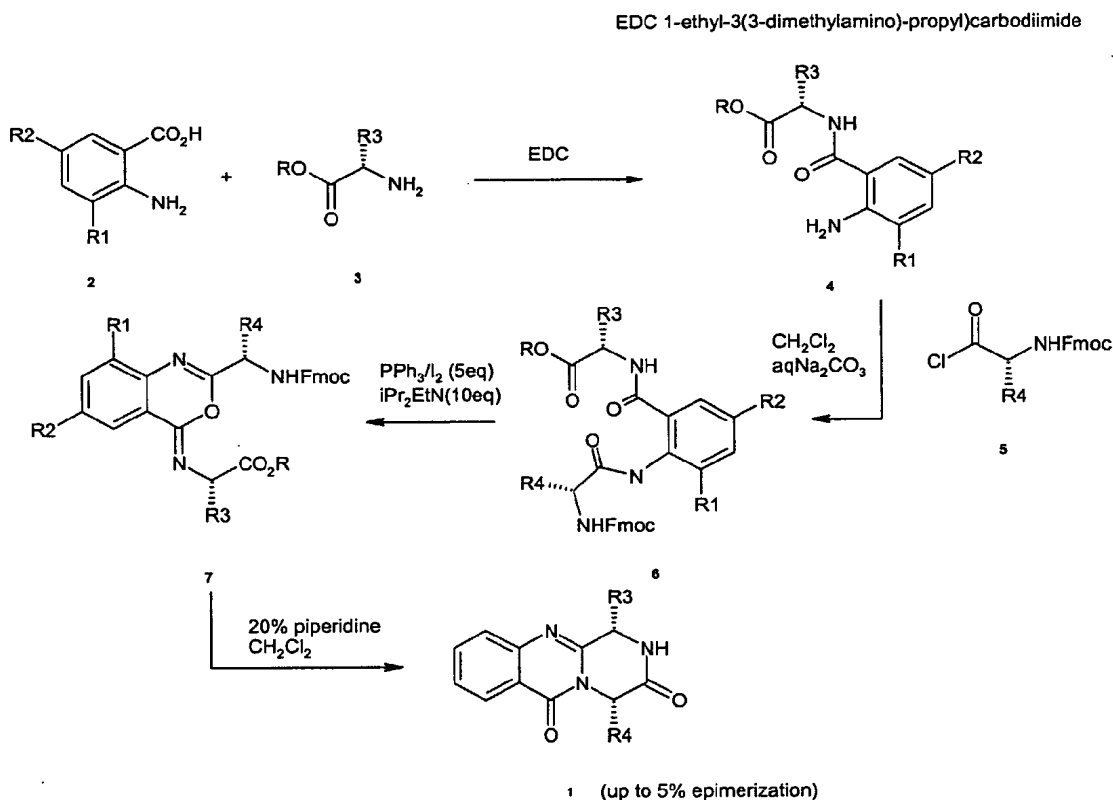
Pyrazinoquinazolinone via benzoxazine intermediate.

The tripeptide 6 is prepared by direct coupling of the amino acid esters (AA-OR) 3 with antranilic acid mediated by EDC. Condensation of 4 with the Fmoc amino acid chloride 5 under two phase Scotten-Bauman condition (CH2Cl2, aq Na2CO3) yields the tripeptide 6. amino acid chlorides 5 are prepared *in situ* by pre-activation of the corresponding Fmoc-AA-OH with BTC (triphosgene) and collidine in THF, DCM or Dioxane [15]. These conditions afford AA Clorides without racemization.

The transformation of the linear tri peptide to oxazine was accomplished using Wip's conditions (PPh3 /I2 /tertiary amine in large excess) Deprotection followed by rearrangement to quinazoline occurred upon treatment with 20% piperidine in methylene chloride . The cyclization to quinazoline is susceptible to steric hindrance and in case of R3,R4 =bulky

groups cyclization requires stronger condition (DMAP reflux CH₃CN). Some epimerization (5%) took place in case in some of the examples.

The application of the s synthesis in solution described above to combinatorical synthesis on solid phase initiates with loading of Wang resin with appropriate amino acid (AA) affording 7. For majority of AA the preloaded Wang resin is commercially available. 7 was deprotected (piperidine in DMF) and appropriate anthranilic acid along was coupled (EDC) to obtain 8(pathway below).
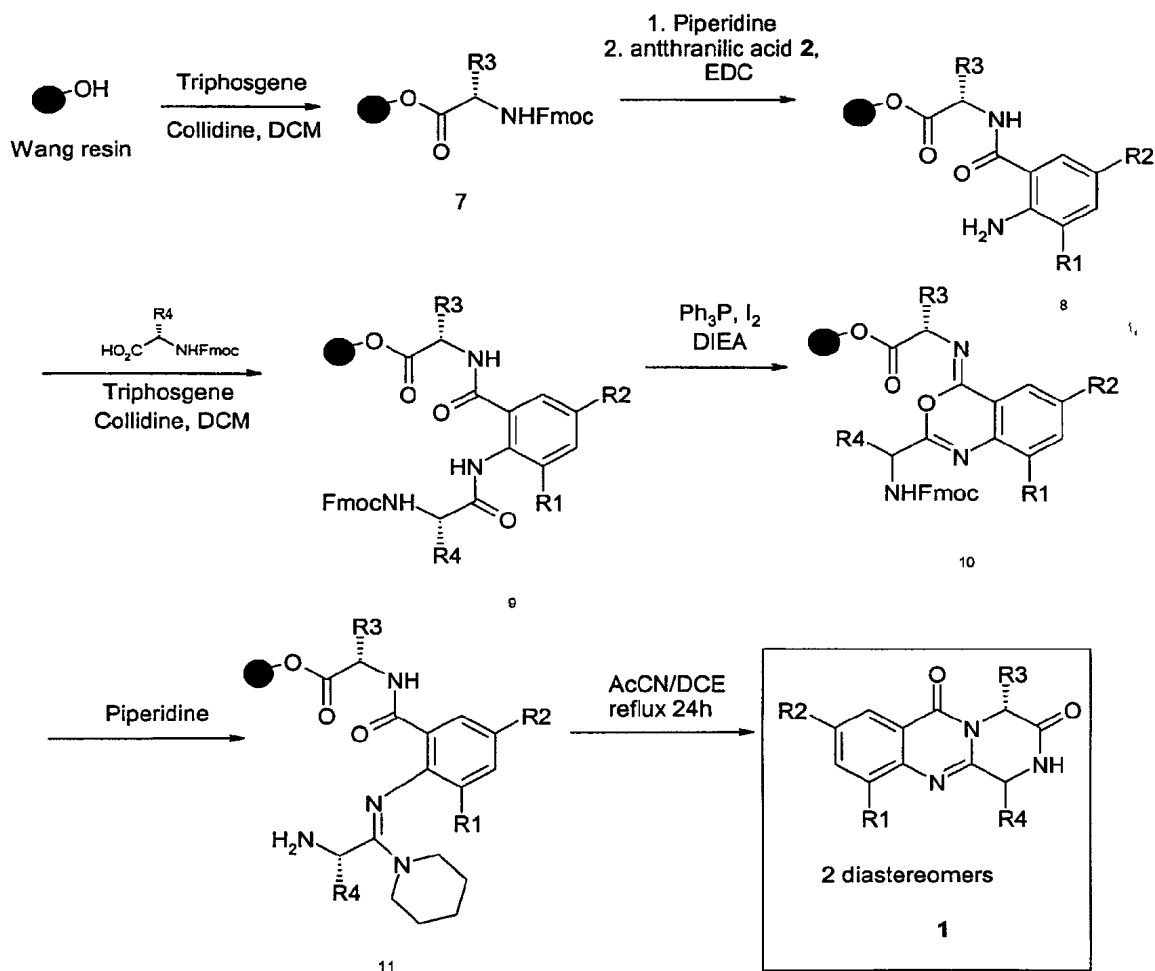
SPS of Pyrazinoquinazolinone

The next step is acylation of aniline 7, with Fmoc –AA-Cl to obtain linear tripeptide 9. The next step is the key dehydrative cyclization of linear tripeptide 9 to 10. To ensure complete conversion, 10 equivalents of Ph₃P were used. The final reaction is piperidine mediated deprotection of Fmoc group and rearrangement of oxazine 10 to amidine carboamide 11. After washing, the resin was refluxed in acetonitrile to induce cyclative cleavage of 11

obtaining the desired pyrazinoquinozaline library **1**. The yields and purity of crude compounds were claimed to be relatively high[14]. Final products **1** can be obtained in few cases as mixture of *cis : trans* diasterioisomers (usually the ratio is 5-8:1). the larger degree of epimerization on solid phase is probably due to the cyclizative cleavage, and HT purifier can separate the products. The above synthesis nicely illustrates the favorable features of the synthetic route. The first two steps involve peptide couplings – the reaction for which SPPS was developed and which proceeds in almost quantitative yield for a variety of amino acids. The dehydration of the liner tripeptide **9** requires large excess of Ph$_3$P, iodine and TEA – reagents which are readily removed by simple filtration on solid phase. The ester functionality undergoing cyclization in the final step was chosen as the position for solid-phase attachment, resulting in self-cleavage from the resin.

The synthesis of pyrazinoquinazoline scaffold requires 3 building blocks the 2 amino acids **3,5** and disubstituted anthranilic acid **2**.

The amino acids and the Fmoc –amino acid are commercial available.

In order to introduce hetero functionalities (NH$_2$, OH) to Pyrazine ring (R3, R4) the synthesis of protected α-hydroxy- AA **14** and α-amino-AA and **12** should be performed . AA **12** is known in literature[16] and the synthesis is illustrated in the pathway below:
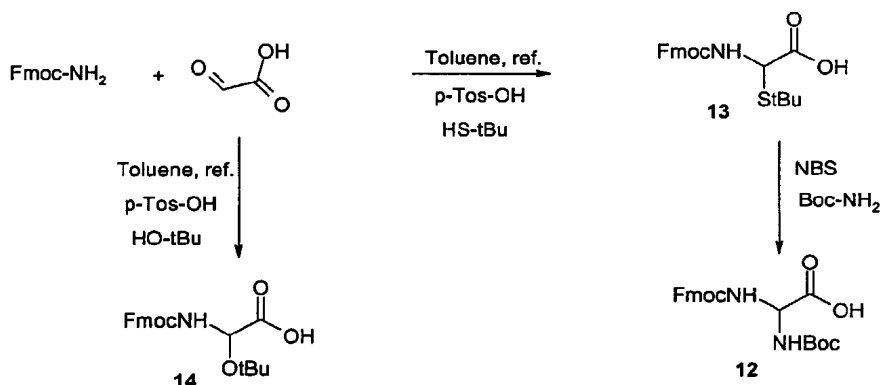

synthesis of protected α-amino-α-OH amino acids

Another AA **14** can be prepared by the similar mode through the condensation between glyoxylic acid and FmocNH$_2$ in presence of *t*-BuOH in boiled toluene affording the desired **14**.

Out of the third building block 3,5 dimethyl anthranilic acid is commercial the other substituted anthranilic acid should be prepared in a tailor-made synthesis .

3-methyl-5-phenyl-anthranilic acid **15** can be prepared by bromination of the commercial available 3-methyl-anthranilic acid **16**[17]. Followed by Suzuki reaction[18] .

Br$_2$, MeOH, AcOH
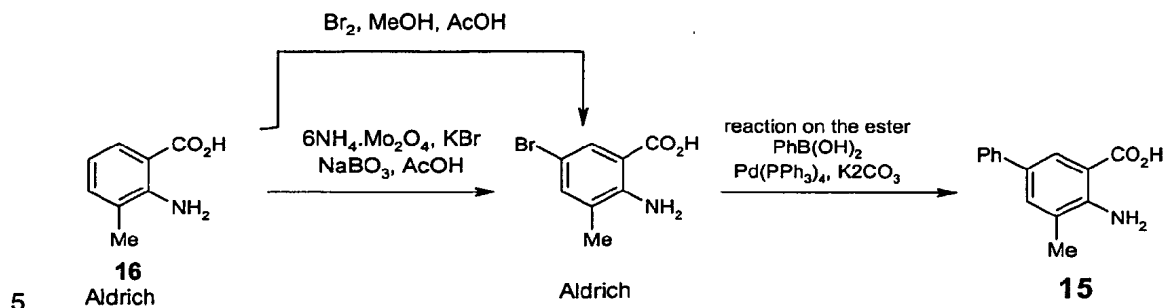
Preparation of 3-methyl-5alkyl or phenyl anthranilic acid

3,5- diphenyl-anthranilic **17** acid will be prepared   from the corresponding dibromoanthranilic acid **18** (commercial) via Pd catalyzed cross coupling reaction with excess of phenyl boronic acid[19] (Aldrich).
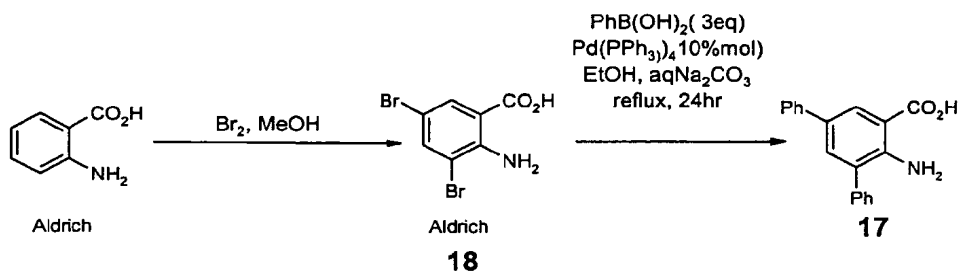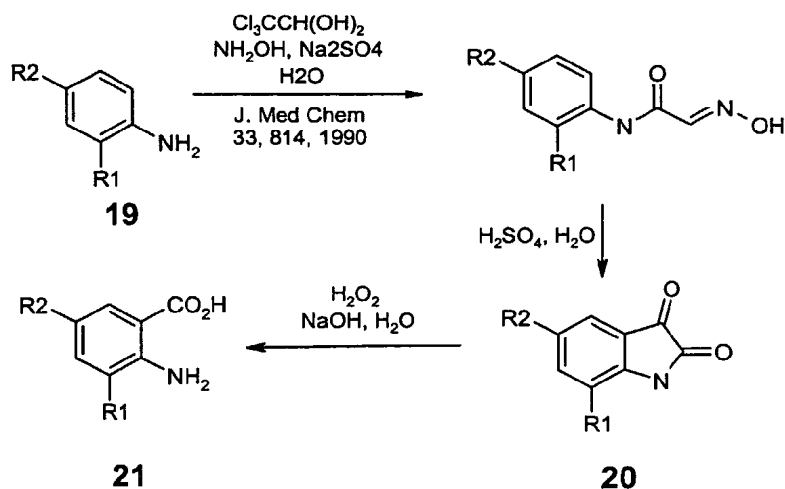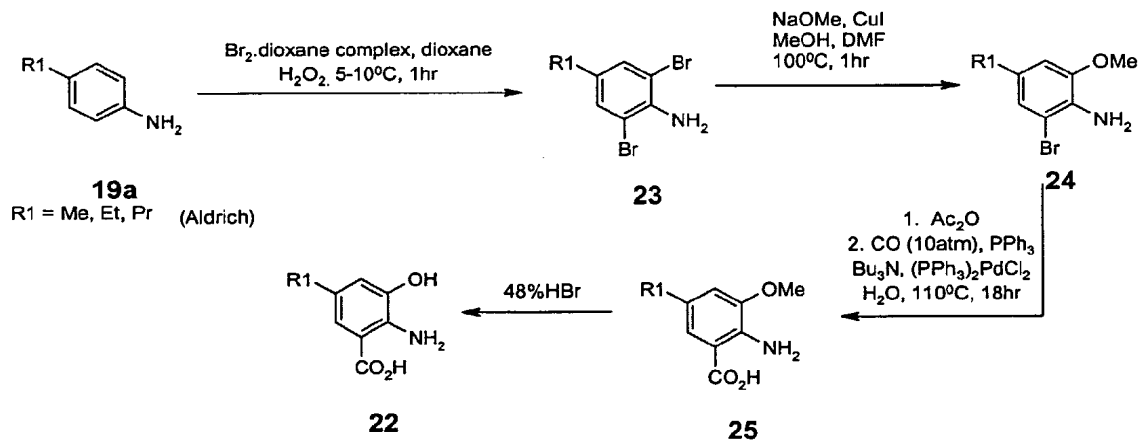

Preparation of diphenyanthranilic acid

Substituted anthranilic acid can also be prepared from the corresponding substituted aniline **19** using a modified Sandmayer methodology. Reaction of the aniline with chloral and hydroxylamine affords the isonitrosoacetanilide followed by cyclization in sulphuric acid yields isatin20. Oxidation of the later with H$_2$O$_2$ affords anthranilic acid [20] **21.** (see pathway below)
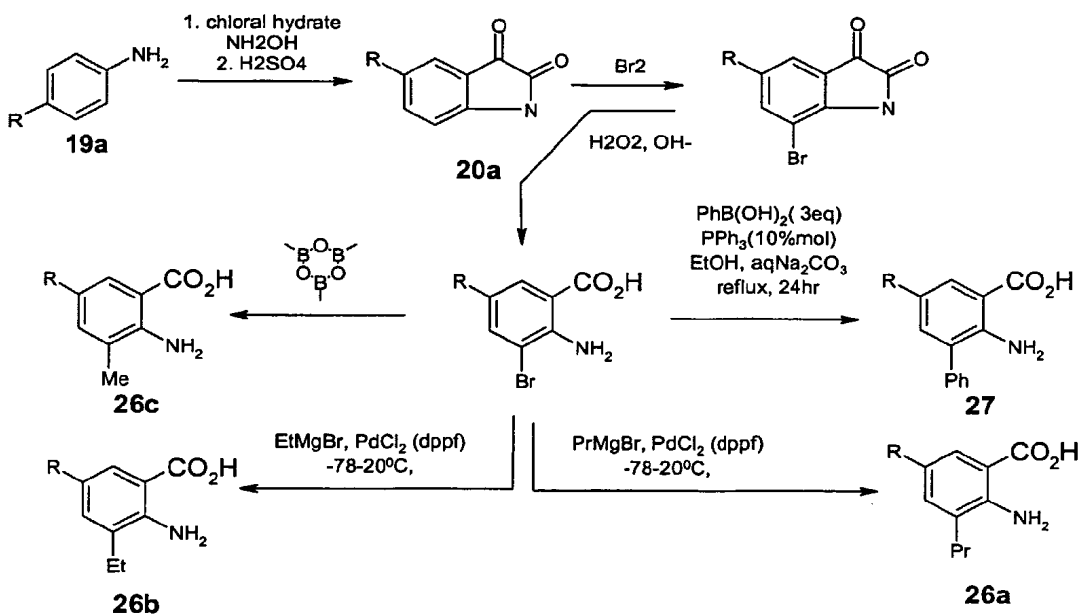
Preparation of anthranilic acids via isatin

Anthralinic acids substituted in position 3 with an OH group **22** can be prepared following

5   the reaction sequence described in the pathway below using 4-substituted anilines (Et, Pr, Me

Aldrich) as starting materials. The aniline was first brominated (**23**) followed by selectively

monomethoxylation in the presence of CuI. The 2-bromo-6-methoxy-4-alkylaniline **24** thus

obtained was carbonylated using Pd complex as catalyst (CO, $Pd(PPh_3)_2Cl_2$) (=> **25**) and the

final step is deprotection by hydrolysis in concentrated hydrobromic acid[21].

Preparation of 3-hydroxy-5-alkyl anthranilic acid

10

4-alkylaniline **19a** can also serve as a starting material for the preparation of dialkyl anthranilic

acid **26** and 5-alkyl 3-phenyl anthranilic acid **27** as described in the pathway below

3-alkyl-5-carboxylanthranilic acid **27** can be prepared starting from o-alkylaniline **19b** that is converted to isatin **20a** (1. chloral, NH2OH, 2. H2SO4), followed by bromination and

5   oxidation to obtain the 5-bromo anthranilate **28** Substitution of the bromo with cyanide (**29**) and hydrolysis affords the 3-alkyl-5-carboxyl-anthranilic acid[22] **27**.
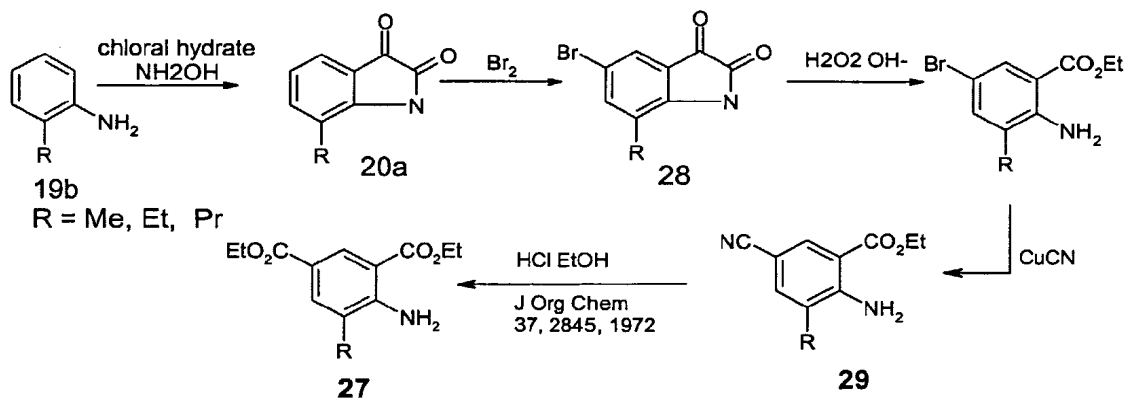

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2. Tetrahedron Asym 11, 3515, 2000

3. Tetrahedron 55 14185 1999

4. Tetrahedron 54, 969, 1998

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22. *Tetrahedron,* 50, 2543, **1994**

16.7 Pyrrole –5 membered ring scaffold

In this chapter is described the comprehensive synthesis of tetra-substituted pyrroles.
The proposed synthetic methods are on Solid Phase (SPS) as well as in solution.

Overview of pyrroles library and sub-libraries
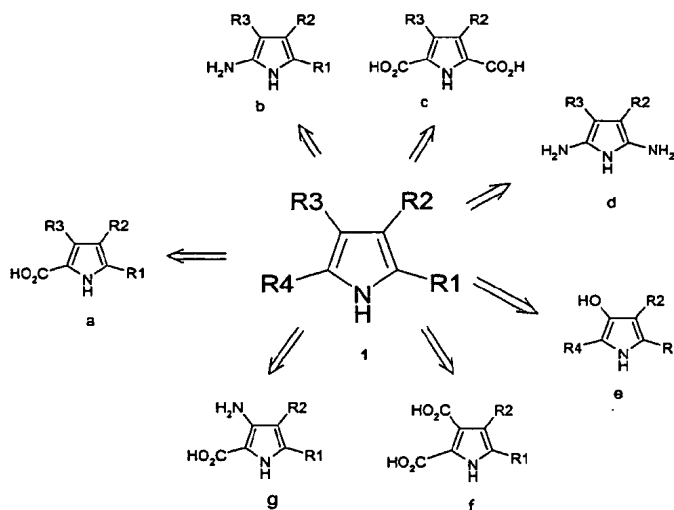
Sub-library **a** which has a carboxyl group at position 2 is prepared in solution. The synthesis
starts from nitrosation of β-keto esters to obtain oximes **3**, which by reductive condensation
with 1,3–diketones lead to ethyl carboxyketopyrrols **5**[1] (pathway below). Pyrroles **5** undergo
reduction of the carbonyl group to methylene[1], following by hydrolysis of ethyl carboxylate to
afford the sub-library **a**. Curtius rearrangement may convert the carboxyl into amine resulting
in the conversion of sub-library **a** to sub library **b** most conveniently. (in case R1 # R2
mixtures of two isomers are obtained and may be separated).
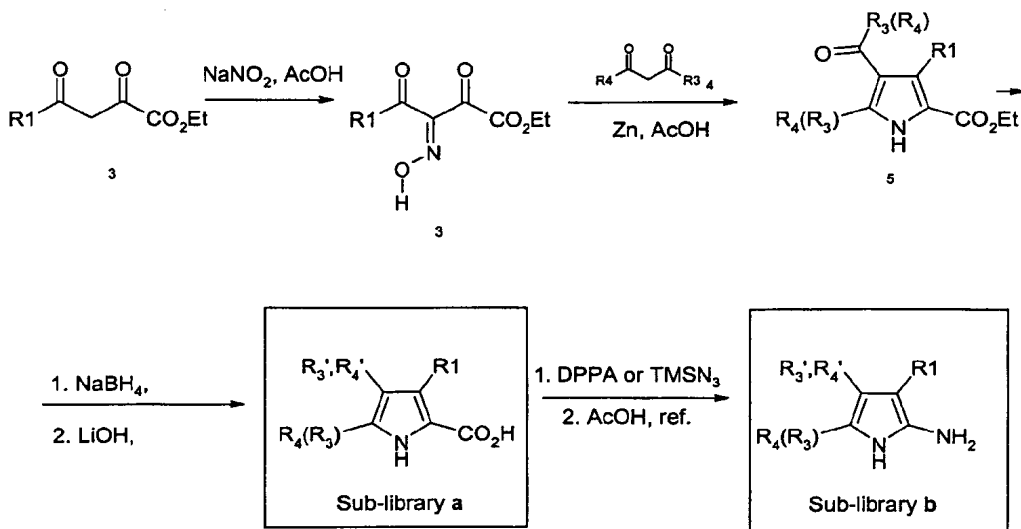
Synthesis of sub-libraries **a, b.**

Two building blocks are required for the synthesis of sub library **a**, and **b**, β-ketoesters, 1,3 diketones which are mostly commercially available.

Compounds of sub-library **c** can be obtained by the synthetic method described in the pathway below. In contrast to the former method this approach involves solid phase synthesis (SPS). Namely: condensation of 1,2-diketones **7** with pre attached Boc imino diacetic acid mono ester **6** as follows:
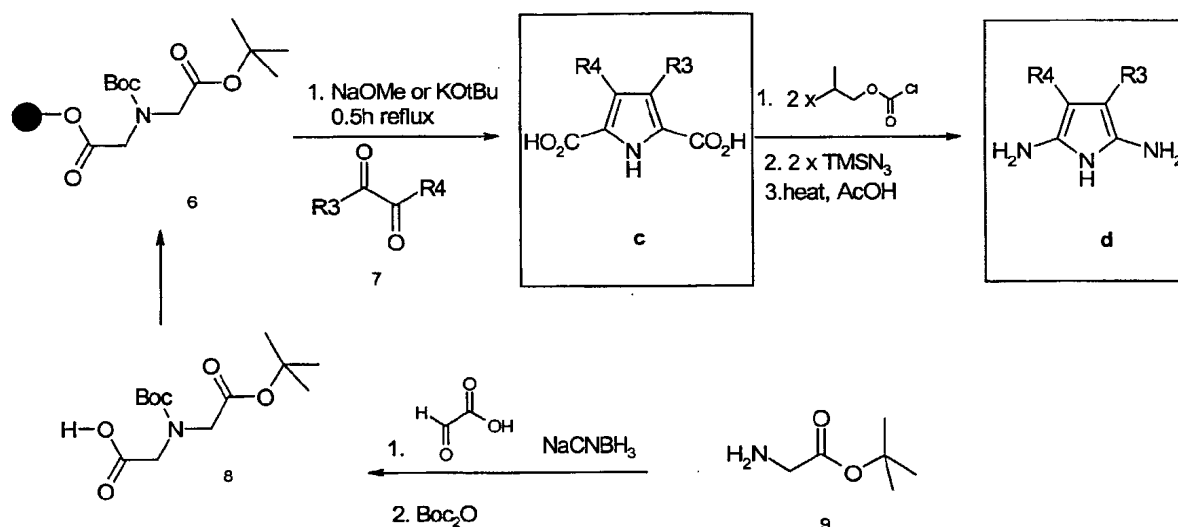
Synthesis of additional ten compounds of category a by SPS.

The reaction[2, 3] is performed under basic conditions using NaOMe or KOtBu. Imino diacetic acid **6** can be easily prepared from t-Bu ester of Gly by reductive amination of Glyoxylic acid using Sodium cyanoborohydride as a reduction reagent and subsequent introduction of a Boc protecting group in multi-gram scale[4].

Sub-library **e** can be prepared using the method described in the pathway below. Position 3 in the resulting products has a fixed subtituent- an hydroxy group. Again, SPS is involved using pre-prepared building blocks as described above.

The process initiates from preparing five acyl Meldrum's acid building blocks (**12**) [5,6] in solution by reaction of acid chlorides **10** with Meldrum's acid **11** to give, in the presence of pyridine the corresponding compound **12** almost quantitatively[7, 8.]

Thus, heating **12** (5 equiv.) with the hydroxyl resin (the resin which generates carboxylic acid, for example the oxime resin[9]) in THF at reflux for a few hours[6] affords the polymer-bound β-ketoesters **13** with concomitant release of CO_2 and acetone, which helps to drive the reaction

to completion. The reaction could be easily monitored by FT-IR on the resin (KBr pellets). The fuctionalization of the α-carbon of **13** is performed with excess of the alkylating reagent, avoiding O-alkylation as well as double alkylation.

Thus, haloalkanes (36 equiv.) in the presence of 1 M TBAF[8] in THF (26 equiv., 3h) easily

5 convert **13** to **14** at RT (Fig.4). Typically it is important to exclude traces of water, which may decrease the yield. Addition of an excess of presynthesized amino ketones **15**[10,11](Fig 5) (20 equiv., 3h, RT), to the resin linked β-ketoesters**14** in THF/trimethylorthoformate (1/1) gives the Shiff bases **16**, Cyclization of **16** under basic conditions with concomitant release of the product **17** into the solution followed by reduction of the ketone (R3 =Me,Et) . (NaBH4

10 BF3OEt2)[1] produces sub library e.
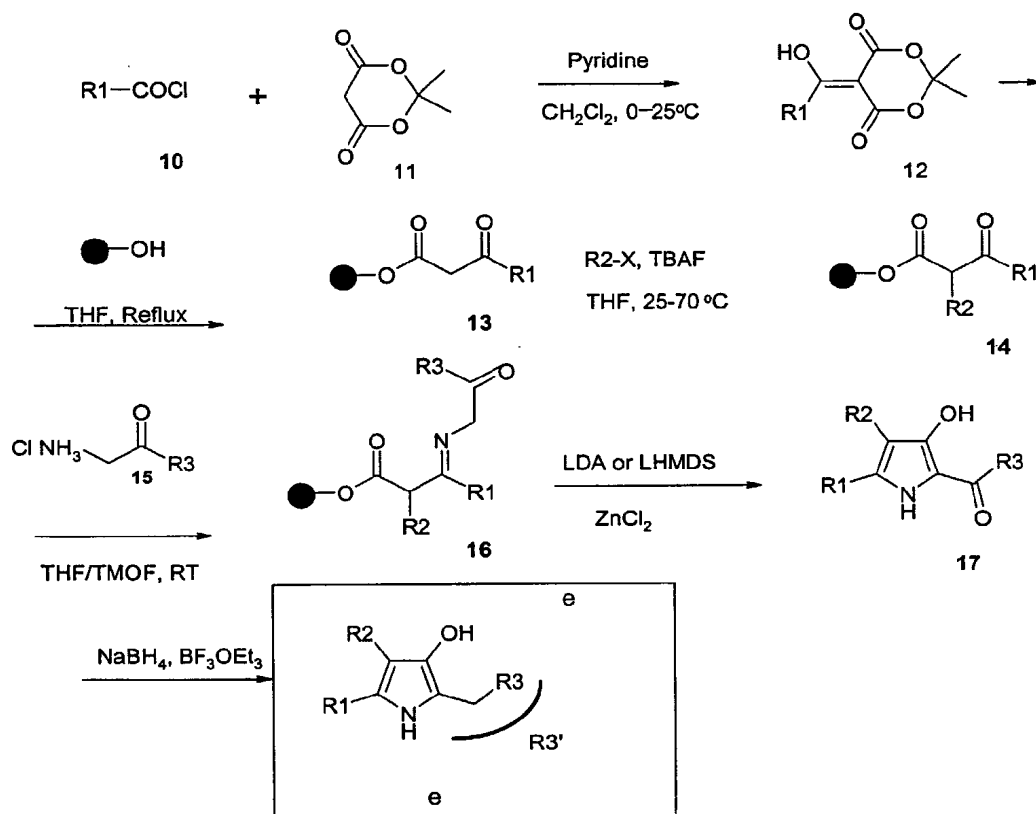
The reaction can also be performed in solution using α-substituted β-ketoesters . following the same reaction sequence.

15 It should be noted that β-hydroxy pyrroles may exist to some extent in its keto tautomer[14] The required building blocks are β-keto esters which are commercial or the α-substituted –β-ketoesters.

The α-aminoketone building block can be prepared from the corresponding amino acid hydroxamate as described in the following pathway.
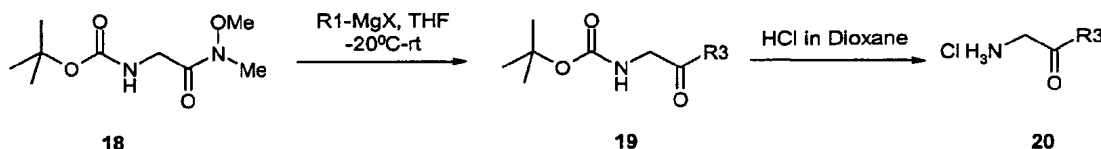

5   Synthesis of amino ketones from Gly Boc hydroxamates.

N-protected glycine recats with N-O-dimethyl hydroxyl amine to give hydroxamte **18**

Reaction of the glycine hydroxamate with Gringard reagent (EtMgBr, MeMgBr) affords the

ketone **19** no over adding is observed. Deprotection of **19** gives the amino ketone building

10   blocks.

In case R3= OH, glycinate reacts with the substituted β-keto esters

Sixteen more products can be obtained by the method described in the pathway below. A key

step for the preparation of sub library f is Michael addition of amino ketones **21** to DTAD

$(21)^{12}$. The obtained aminoolefine **23** undergoes cyclization in acidic conditions, to afford the

15   sub-library f.
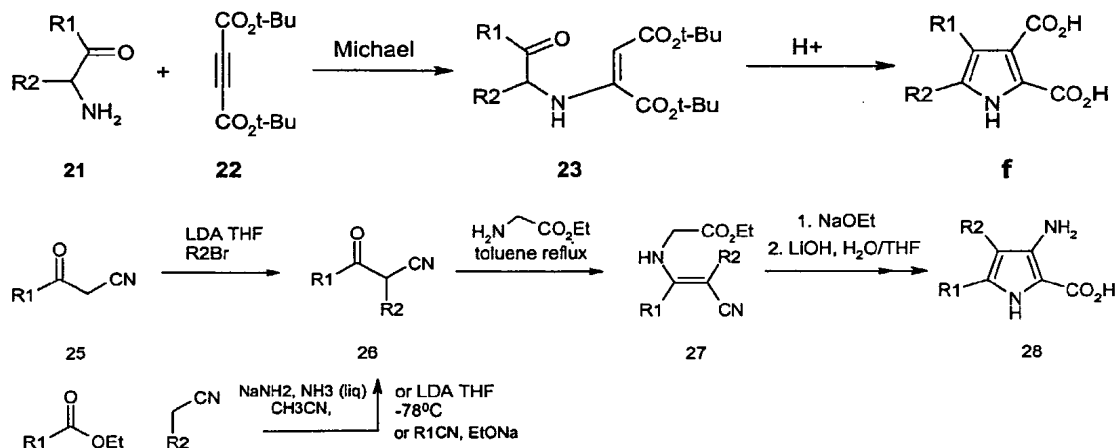
synthesis of 2-carboxy-3-amino-pyrroles

**20**   The synthesis of 2-carboxy, 3-amino pyrroles **28** is well known[12, 13] (see pathway above). It is

performed through the enamine formation of **26** and subsequent intramolecular cyclization of

27 under basic conditions (NaOEt) to give **28**. The β-keto nitriles **25**. can be prepared by

either alkylation of **25**[15] or acylation of the corresponding nitrile.[16]

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16.8 Thiophenes and related scaffolds

The chemistry of 2-aminothiophenes and related scaffolds has attracted special attention in the last 30 years because of their applications in pharmaceuticals, agriculture, pesticides and dyes.
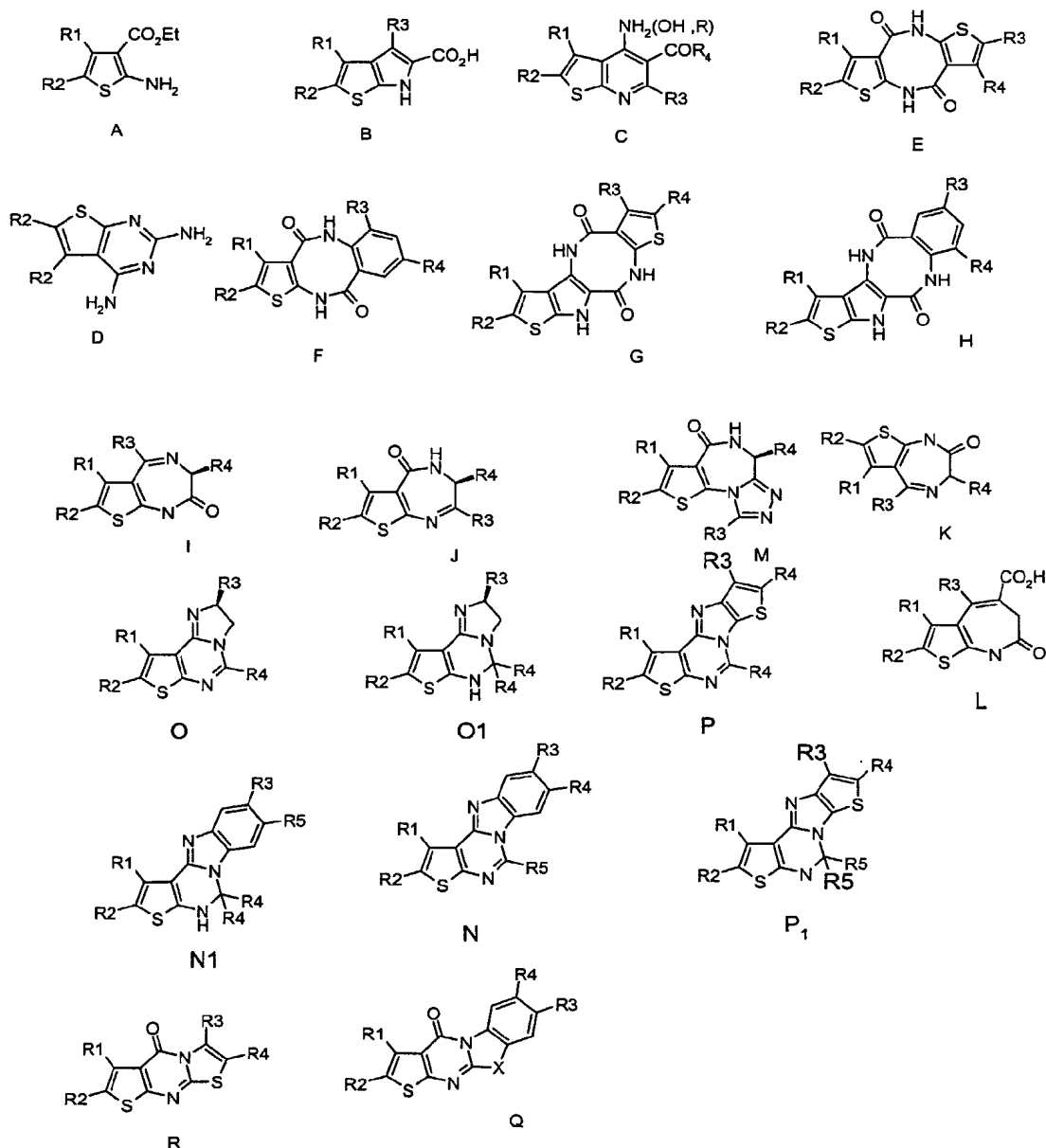

The chemistry of 2-aminothiophenes are conveniently available through the, synthetic method developed by Gewald [1ab] who devised the most facile and promising synthetic route leading to 2-aminothiophenes A with electron withdrawing substituents such as cyano, carbethoxy *etc.* in the 3- positions and alkyl, aryl, cycloalkyl, and hetaryl groups in the 4- and 5- positions.

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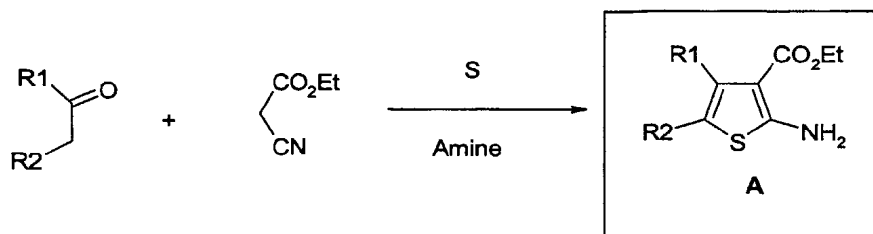
Gewald reaction

The simplest version of the Gewald reaction consists of a one-pot procedure, namely

5   condensation of aldehydes, ketones or 1,3-dicarbonyl compounds with activated nitriles and

sulfur in the presence of amine at room temperature. Ethanol, DMF, dioxane are preferred

solvents and amines like diethylamine, morpholine, or triethylamine have been used [1-7] This

method offers considerable improvement over other methods by replacing an a-

mercaptoaldehyde or an a- mercaptoketone by simpler starting materials. It is necessary to use

10   0.5-1 molar equivalents of amine based on the amount of nitrile to obtain high yield.

In another synthesis version a two-step procedure is preferred. An a,b-unsaturated nitrile is

first prepared by a Knoevenagle-Cope condensation and then treated with sulfur and an amine.

This two-step version of the Gewald reaction gives higher yields. Alkyl aryl ketones do not

give thiophenes in the one-pot modification, but gives acceptable yields in the two-step

15   technique[2] (see pathway below).
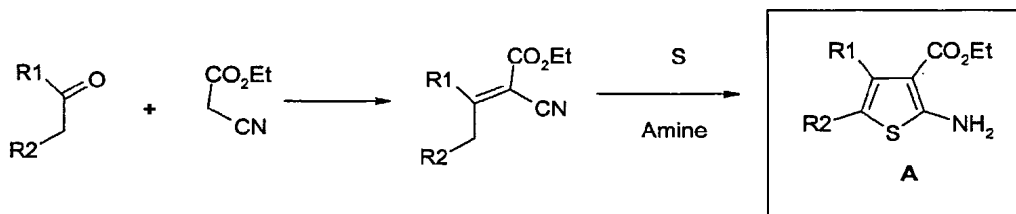
Two step Gewald reaction

The use of t-butyl cyanoacetate instead of the ethyl ester enables to obtain free acid of 3-

20   carboxy-2-aminothiophenes by convenient TFA/DCM hydrolysis[8]

The amino acid obtained as well as the protected acid can be used as building blocks for

further transformation to more complex scaffolds as is exemplified below:

16.8.1 5, 5 bicyclic scaffolds

Thienopyrrole synthesis
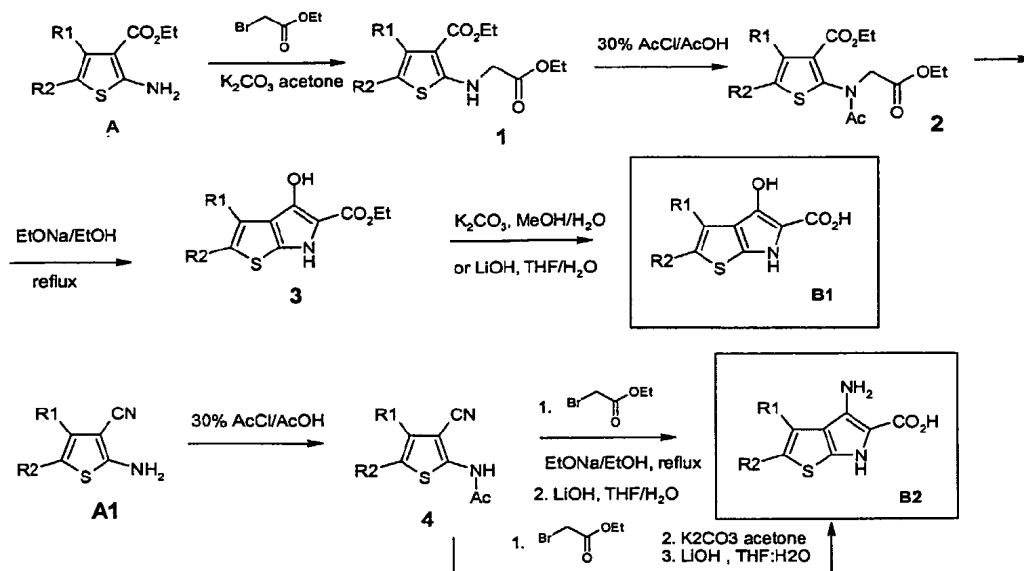
5   Thienopyrrole scaffold B[9] (pathway above) is prepared by the reaction of aminocarboxylate A
with bromoacetate (K_2CO_3) to obtain diester intermediate 1, which after acetylation
(compound 2) (30% AcCl in AcOH) undergoes Dieckmann condensation (EtONa, EtOH) to
afford 3-hydroxy-2-carboxy thieno[2,3-b]pyrrole B1. The amino analog B2 requires starting
with the 2-amino-3-cyano thiophene A1. Acetylation followed by alkylation with a-

10   bromoacetate (K2CO3 acetone or NaH DMF) leads under similar reaction conditions to ring
closure producing 3-amino-caboxy thienopyrrole B2. Acetylation of the amine at position 2
and LiOH are required to increase the nucleophilicity of the amine .

16.8.2 5,6-bicyclic scaffolds

The thienopyridine scaffold C is prepared via modified Friedlander reaction , namely reaction

15   of thiophene A, A1 and 5 with b-ketoesters , 1,3 diketones under basic condition to form
thienopyridines as described in the pathway below
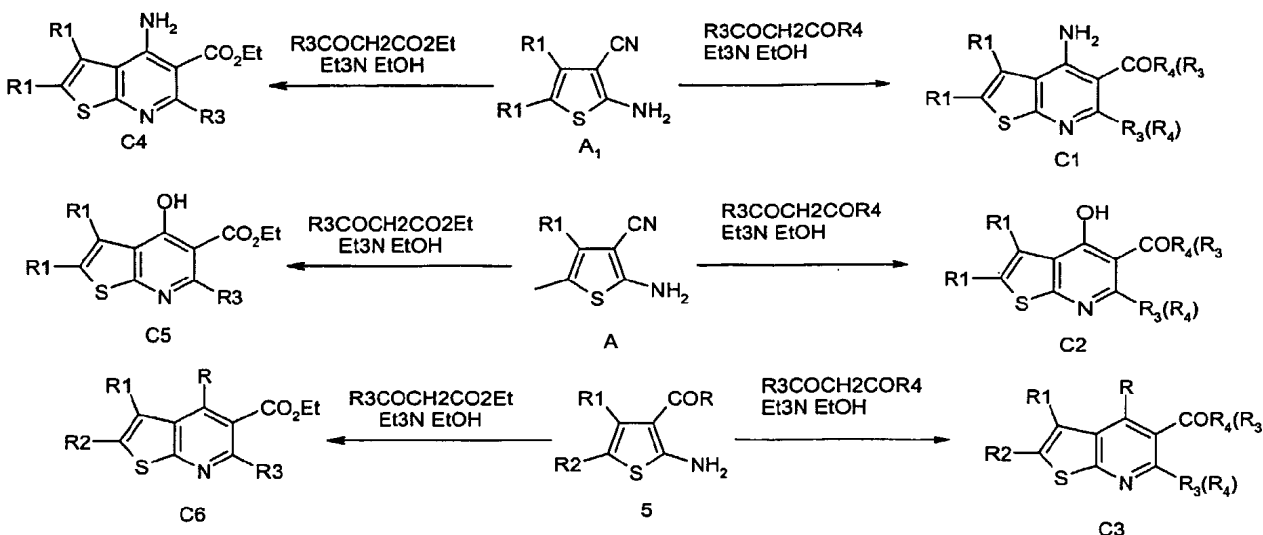
Thienopyridine synthesis

Another 5,6-bicyclic ring system – the thieno pyrimidine D is prepared by the reaction of

5   thiophene A ,A1 with chloro formamidine hydrochloride 4, 11
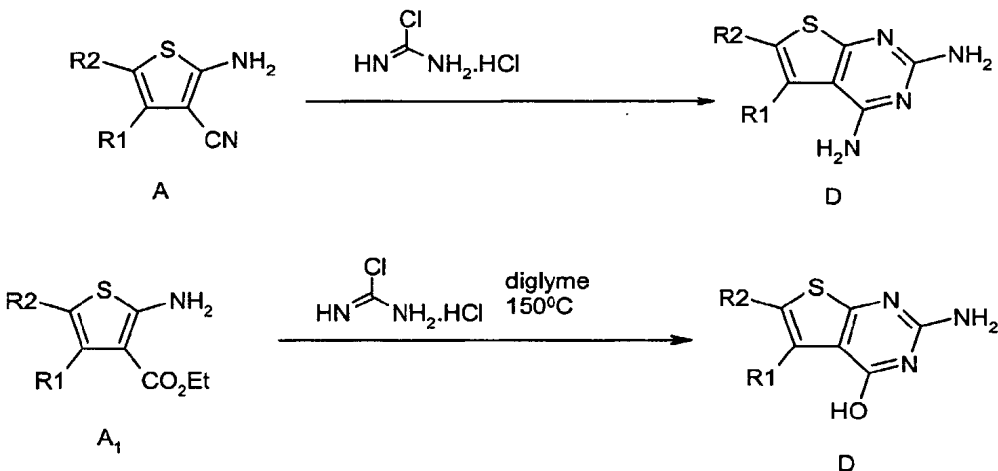
Thienopyrimidine synthesis

16.8.3 5,8,5 5,8,6 tricyclic and 5,5,8,6 5,5,8,5 tetracyclic scaffolds

The scaffolds E,F G and H can be generated from thiophenes are described in scheme 6. These

10   compounds result from the formation of an eight membered ring Dilactam.

preparation of 8 membered ring dilactam
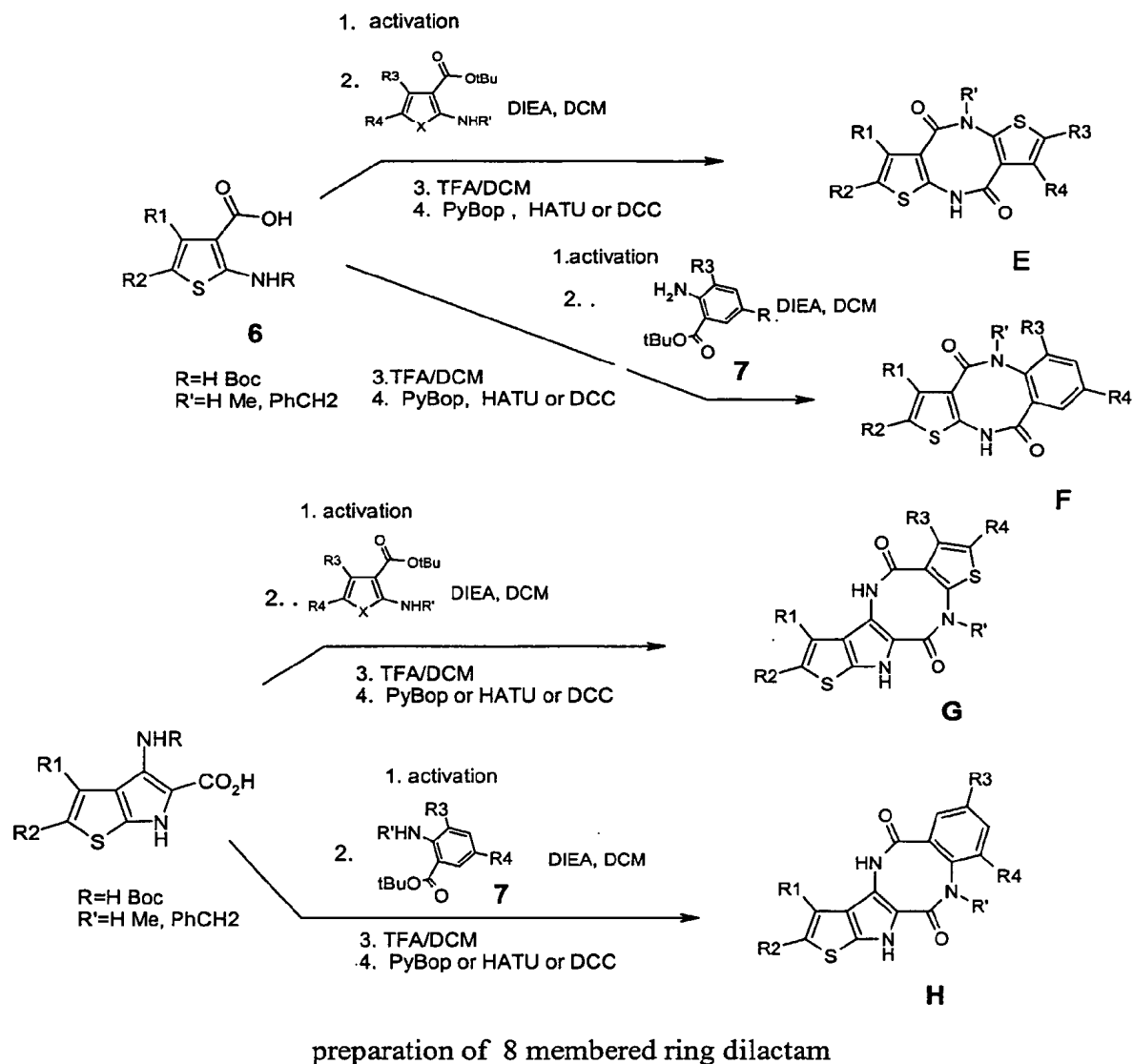
The formation of the eight membered ring includes several steps:

1. Activation of the β–amino acid using SOCl2[12a] or POCl3[12b](in these cases the amine should be protected by Boc) or by DCC[12c] and methyl chloroformate[12d]

2. Coupling of the activated acid and another N-protected β-amino-t-butyl ester[13,]

3. Deprotection of the t-butyl ester and the N-Boc amine using TFA in DCM

4. Coupling by PyBop or any other analog in case R' is a benzyl group it can be removed at this stage by hydrogenation.

16.8.4 5,7 bicyclic scaffold

The synthesis of I, J analogs of the benzodiazepines scaffold is illustrated in the following pathway. In both approaches chiral amino acid are introduced into the synthesis raising the

diversity around the α carbon. Thieno diazepine I is prepared from 2-amino-3-acyl)-
thiophenes 5. which reacts with pre formed Boc amino acid chloride (amino acid, BTC,
collidine, THF or DCM). Deprotection of 8 (4N HCl) with concomitant ring closure leads to
2-oxothienodiazepine I. Thiophenodiazepine J can be prepared starting from 2-amino-3-
carboxy-thiophenes A, which after pre activation to the thienooxzaine dione (BTC, collidine,
THF or DCM)) reacts with amino ketone to obtain 9, ring closure afford 5-oxothienodiazepine.
J[14]


synthesis of thienodiazepines

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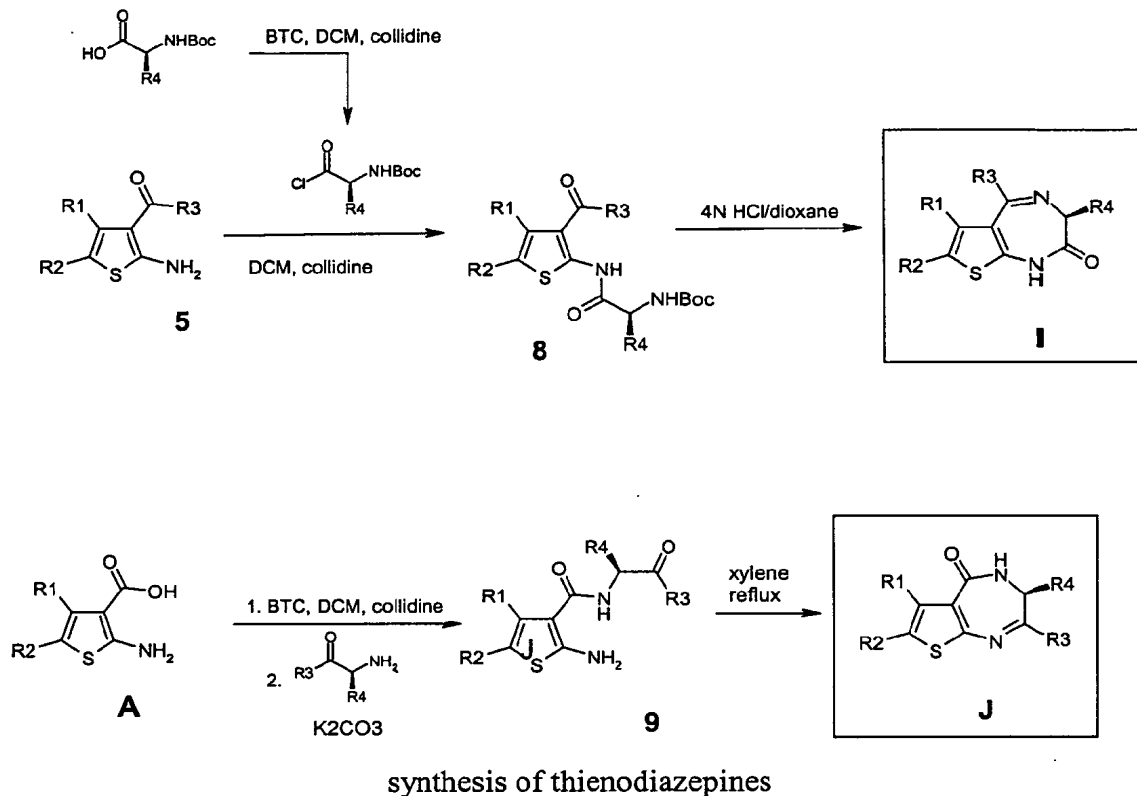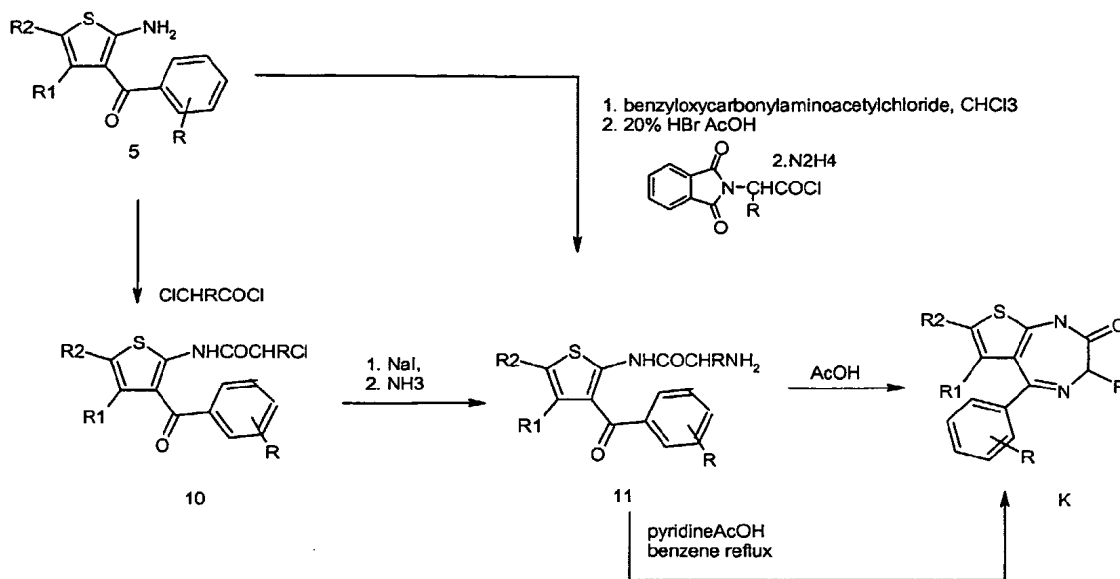
The synthesis of thienodiaepine K

The synthesis of thienodiazepine K is described in the above pathway. 2-amino-3-acyl thiophene 5 is first acetylated with the appropriate α-haloacetyl chloride Nucleophilic substitution with NaI followed by ammonia to obtain the amino amide[15] 11. The latter undergoes ring closure to the thienodiazepine K under acidic conditions Another alternative is to react thiophene 5 with the phthalide protected amino acyl chloride, Deprotection with hydrazine (11) and ring closure to obtain thienodiazepine K [16]

The synthesis of thienozepine L is based on coupling of sucssinic anhydride or acid chloride monoester with thiophene 5 (see pathway below) The obtained amide 12 undergoes intramolecular condensation (NaH) to provide the targeted compounds[17].
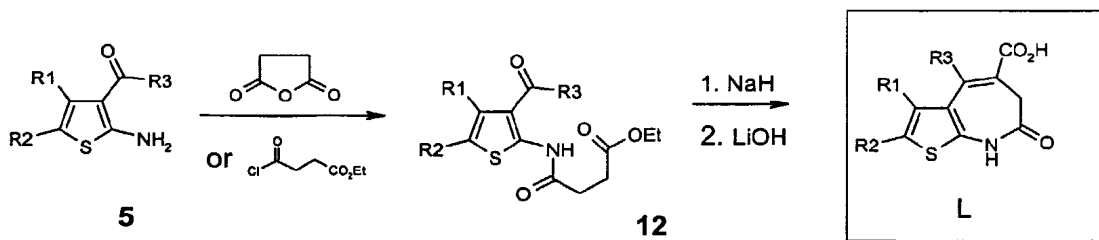
preparation of thienozepine

Scaffold M, having a thienodiazepinone skeleton may be prepared as described in the pathway below. The N-protected aminocarboxythiophene A is first preactivated (BTC, collidine, DCM) and submitted to reaction with α-amino acetonitriles 14 to afford amide 13.

The latter reacts under basic conditions (NaOMe) to provide through the intramolecular cyclization the disubstituted intermediate 2-aminothieno-1,4-diazepin-5-one 15[18]. In the next step 2-aminothieno-1,4-diazepin-5-one 15 is heated with acetyl hydrazine leading to thienotriazolodiazepinone M
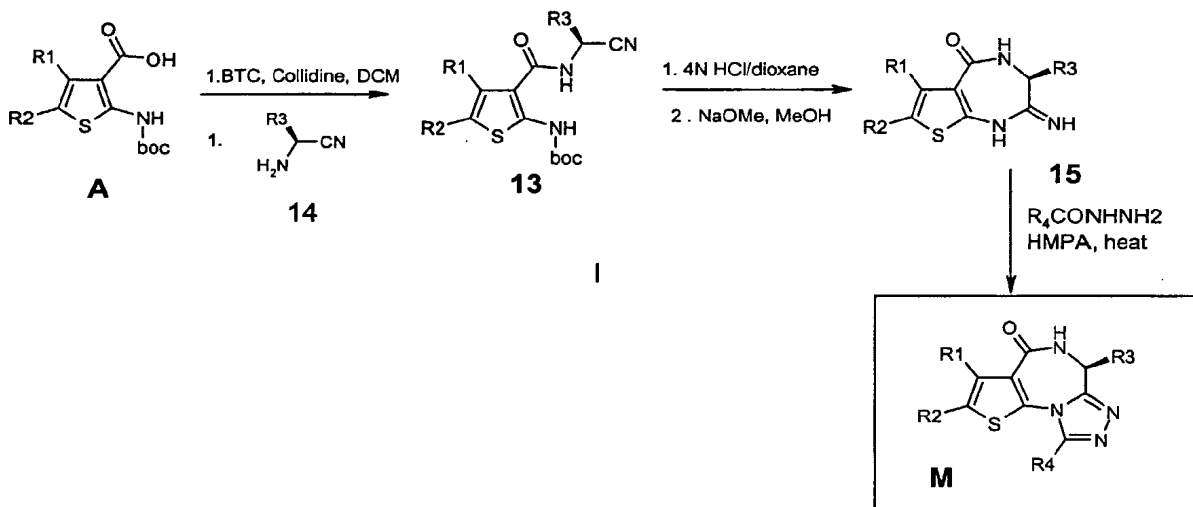

The synthesis of thienotriazolodiazepinone

16.8.5 5,6,5,6 Tetracyclic and 5,6,5 tricyclic scaffolds

The thiophene substituted in the 3 position with a benzimidazole namely benzimidazoloaminothiophene 16 can serve as a building block for the synthesis of thieno(2',3',4,5)pyrimidino(1,6)benzimidazole,N N1, The starting material 2-cyanomethylbenzimidazole 16,is prepared from substituted phenylene diamine 17 and malononitrile [19] Nitrile 18 is submitted to Gewald reaction using elemental sulfur powder and ketones [20] or cyanoacetamide [21] in dry DMF containing a catalytic amount of TEA under reflux to form thiophene 16 (see pathway below).
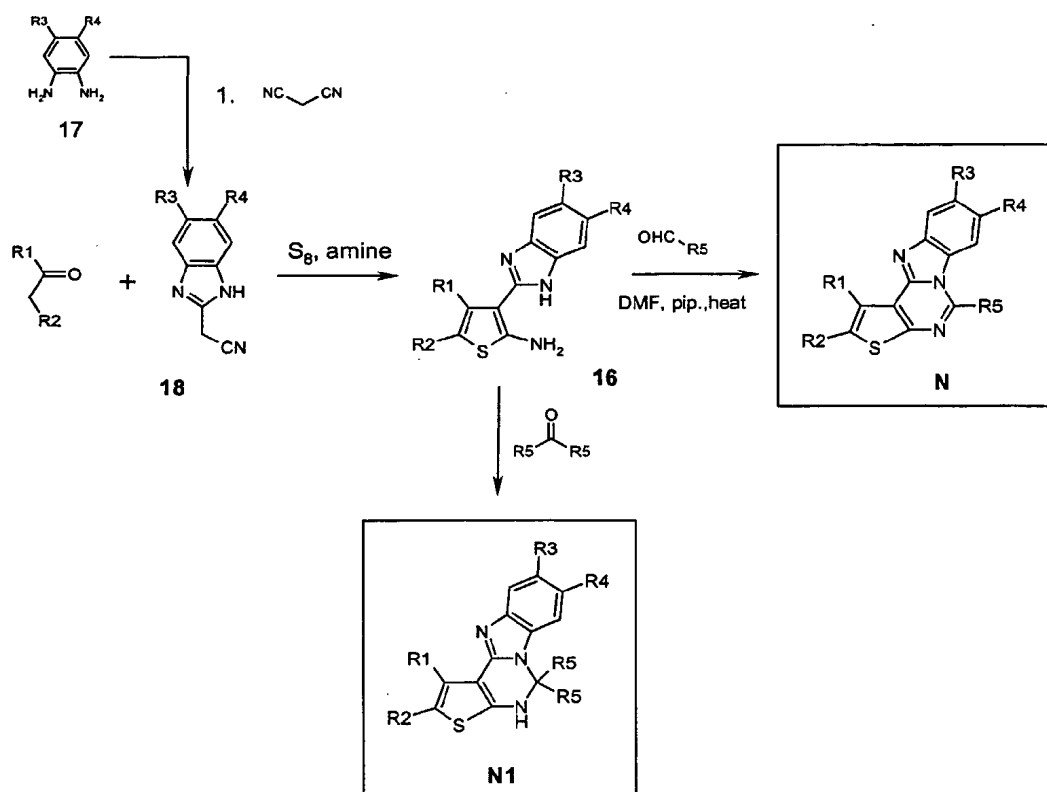
The synthesis of thienopyrimidinobenzimidazole

Condensation of 16 with aldehydes or ketones, afford N and N1 respectively [21, 22].

20   **19**   **O**

O1
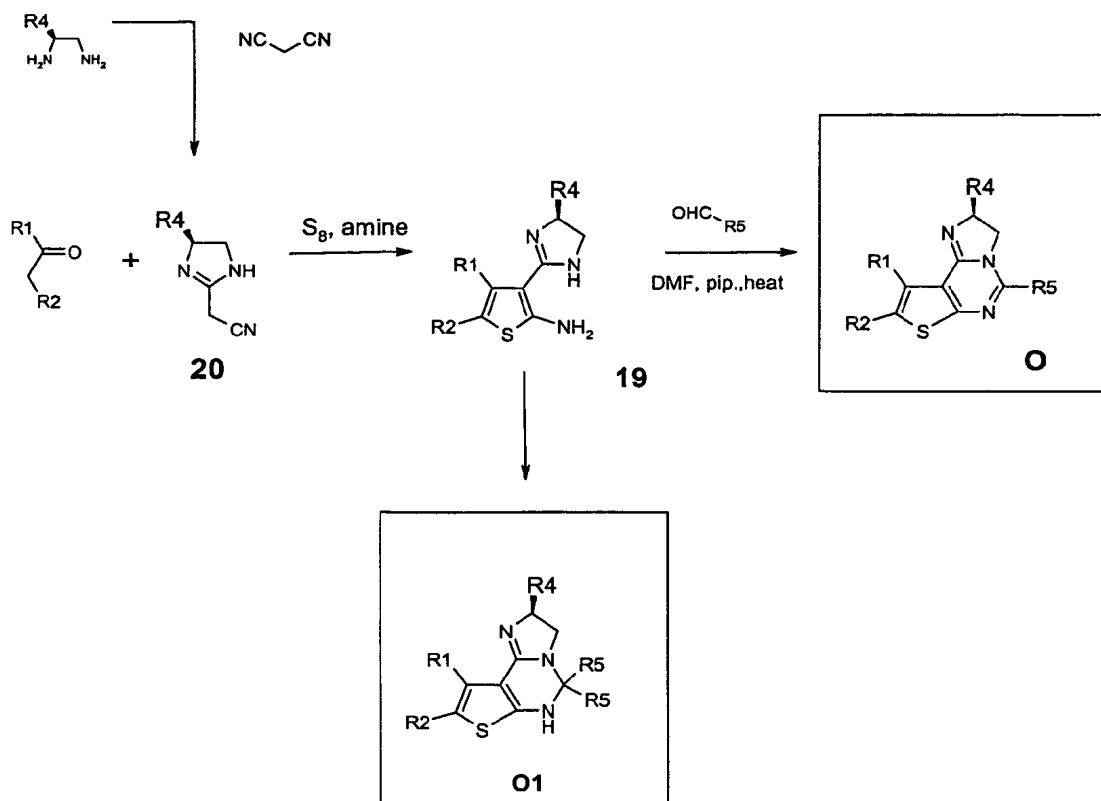
The synthesis of thienopyrimidinodihydroimidazole

Using the same approach dihydroimidazoylacetonitrile 20 [23] (see pathway above) and
5   thienoimidazoyl-acetonitrile 21 (see pathway below) can be prepared   from the corresponding
diamines (ethylene diamine and thiophene2,3 diamine[24]) and malonolitrile The resulting
nitriles react with ketones under Gewald conditions forming O, O1 and P, P1.

21   **22**   **P**

P1
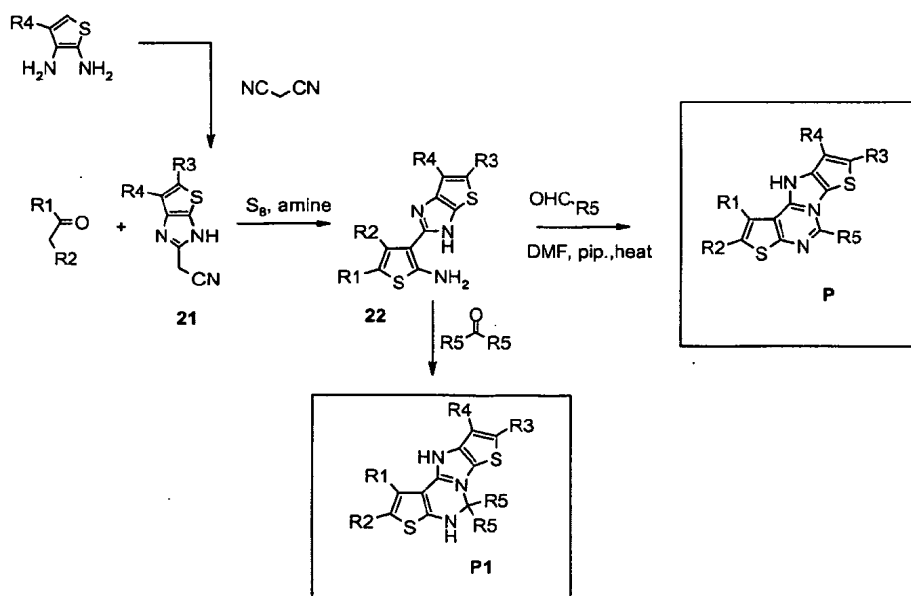
The synthesis of scaffolds P and P1

16.8.6 5-6-5-6 tetracyclic scaffold

A   X = S or N
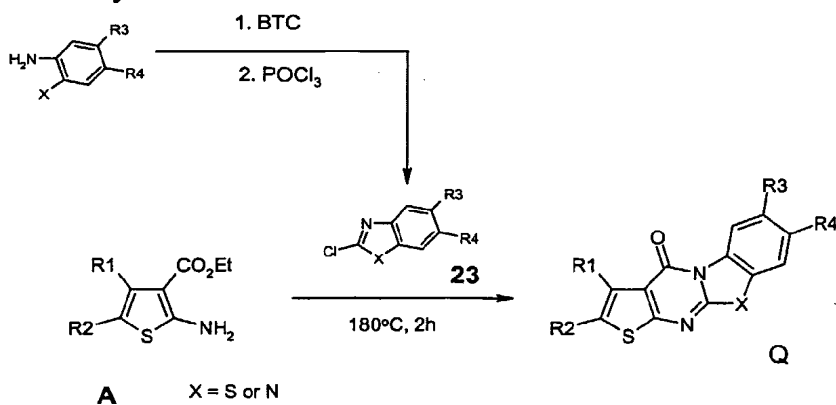
5   synthesis of scaffold Q

4H-thieno[2',3':4,5]pyrimido[2,1-b]benzothia-or--zoles Q can be prepared from amino thiophene A as outlined in the pathway above.[25] 2-Amino-3-carboxythiophene undergoes condensation at high temperature with chlorobenzimidazole[26]. chlorobenzthiazole 23 leading

10   to the corresponding thienopyrimidinazoles Q.

16.8.7 5-6-5 tricyclic scaffold

Thia-triaza-s-indacenone R (see pathway below), can be obtained according to literature procedures In this synthesis the aminothiophene   A undergoes cyclization in boiling acetic acid with pre formed methylthio imidazoles 24 to give the desired system. R

15

References

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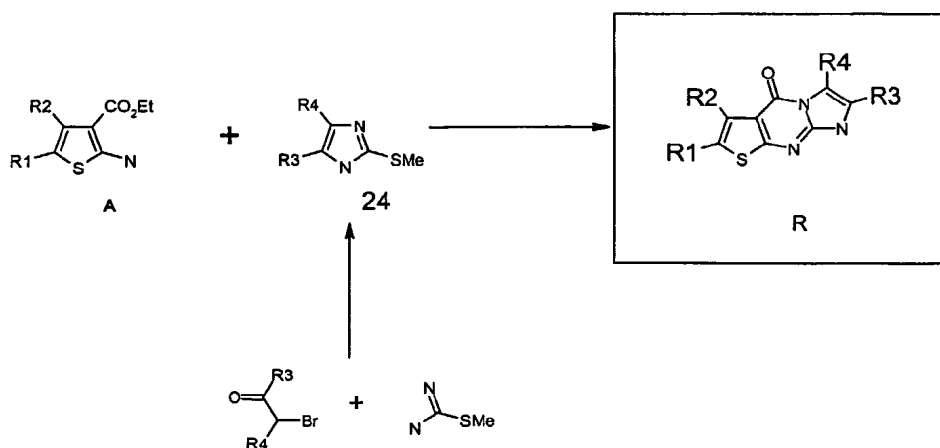
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It will be appreciated that the above described methods of target measurement and drug discovery may be varied in many ways, including, changing the order of steps, which steps are performed on-line and which steps are performed off-line. In addition, various parallel and/or

5   sequential configurations may be used to implement the above invention, optionally utilizing a variety of software tools and/or various hardware/software combinations. In addition, a multiplicity of various features, both of methods and of devices has been described. It should be appreciated that different features may be combined in different ways. In particular, not all the features shown above in a particular embodiment are necessary in every similar exemplary

10 embodiment of the invention. Further, combinations of the above features are also considered to be within the scope of some exemplary embodiments of the invention. Also within the scope of the invention are computer readable media on which software, for performing part or all of an exemplary embodiment of the invention, are written. It should also be appreciated that many of the embodiments are described only as methods or only as apparatus. The scope of the

15 invention also covers hardware and/or software adapted and/or designed and/or programmed to carry out the method type embodiments. In addition, the scope of the invention includes methods of using, constructing, calibrating and/or maintaining the apparatus described herein. Headers, where they appear, are provided for ease of browsing and should not be construed as necessarily limiting the contents of the section to that which is suggested by the heading. When

20 used in the following claims, the terms "comprises", "comprising", "includes", "including", "having" or their conjugates mean "including but not limited to".

It will be appreciated by a person skilled in the art that the present invention is not limited by what has thus far been described. Rather, the scope of the present invention is limited only by the following claims.

CLAIMS

1.   A method of obtaining information about a chemically active area of a target molecule, comprising:

        providing a set of substantially rigid chemical gauges;

        reacting said target with a plurality of gauges of said set of gauges;

        assaying a binding of said gauges with said target to obtain a plurality of assay results; and

        analyzing said assay results to obtain information about said chemically active area.

2.   A method according to claim 1, wherein said gauges allow rotation of moieties of said gauges.

3.   A method according to claim 1, wherein said gauges are constructed using a rigid scaffold.

4.   A method according to claim 1, wherein constituent atoms of said gauges do not move more than 1 Å unless at least 20Kcal/Mol are applied to the gauge.

5.   A method according to claim 1, wherein analyzing comprises identifying a plurality of spatial and chemically specific bindings configurations in said target active area.

6.   A method according to claim 5, wherein said configurations comprise triangular configurations.

7.   A method according to claim 5, wherein identifying comprises identifying a configuration that matches a configuration of a bound gauge.

8.   A method according to claim 5, wherein identifying comprises identifying a configuration that does not match a configuration of a bound gauge.

9.   A method according to claim 8, wherein identifying comprises identifying by statistical analysis of said assay results.

10.   A method according to claim 9, wherein identifying comprises identifying by clustering.

5   11.   A method according to claim 5, wherein identifying comprises assuming each gauge indicates a single configuration.

12.   A method according to claim 5, wherein identifying comprises assuming at least some of the gauges indicate a plurality of configurations.

10

13.   A method according to claim 5, wherein identifying comprises classifying gauges by chemical moieties at vertexes of said configurations.

14.   A method according to claim 1, comprising reconstructing a spatial map of at least part

15   of said chemically active area, from at least two of said assay results, said part including at least four chemical binding areas.

15.   A method according to claim 14, wherein said part includes at least six chemical binding areas.

20

16.   A method according to claim 5, comprising reconstructing a spatial map of at least part of said chemically active area, from at least two of configurations, said part including at least four chemical binding points.

25   17.   A method according to claim 16, wherein said part includes at least six chemical binding areas.

18.   A method according to claim 16, wherein reconstructing comprises:
       test-reconstructing a plurality of spatial maps from said configurations;
30   scoring said maps; and
       selected a spatial map based on its score.

19.   A method according to claim 16, wherein reconstructing comprises:

test-reconstructing a plurality of spatial maps from said configurations;

clustering said maps according to common substructures; and

selected a spatial map based on a relative property of a cluster it belongs to.

5 20. A method according to claim 19, wherein said relative property comprises size.

21. A method according to claim 16, wherein said spatial map includes enough binding points to ensure binding of a small molecule drug having a chemical profile matching the binding points.

10

22. A method according to claim 21, wherein said spatial map includes at least 6 binding points.

23. A method according to claim 21, wherein said spatial map includes at least 8 binding

15 points.

24. A method according to claim 1, wherein said set of gauges comprises a set of gauges with at least 10,000 gauges.

20 25. A method according to claim 1, wherein said set of gauges comprises a set of gauges with at least 50,000 gauges.

26. A method according to claim 1, wherein said gauges comprise moieties arranged in spatial configurations and wherein said gauges are selected to span a virtual space of spatial

25 chemical configurations.

27. A method according to claim 1, wherein substantially each point of virtual space that is spanned by said gauges is covered by at least two gauges.

30 28. A method according to claim 1, wherein substantially each point of virtual space that is spanned by said gauges is covered by at least three gauges.

29.   A method according to claim 1, wherein at least 0.5% of said gauges bind with said target.

30.   A method according to claim 1, wherein at least 1% of said gauges bind with said target.

31.   A method according to claim 1, wherein at least 3% of said gauges bind with said target.

32.   A method according to claim 1, wherein at least 50% of said gauges are defined by adding moieties to a set of fewer than 100 scaffolds.

33.   A method according to claim 1, wherein at least 50% of said gauges are defined by adding moieties to a set of fewer than 50 scaffolds.

34.   A method according to claim 1, wherein at least said set of gauges uses fewer than 15 different chemical moieties to define the chemical behavior of said gauges.

35.   A method according to claim 1, wherein at least said set of gauges uses fewer than 10 different chemical moieties to define the chemical behavior of said gauges.

36.   A method according to claim 1, wherein said assay is a functional assay.

37.   A method according to claim 1, wherein said assay is a binding assay.

38.   A method according to claim 1, wherein said assay is a cellular assay.

39.   A method according to claim 1, wherein said assay is a flow-through assay.

40.   A method according to claim 36, wherein said functional assay is performed in the presence of a natural substrate of said target.

41.   A method according to claim 1, wherein said target comprises a protein including a biochemically active area adapted to engage a substrate.

42.   A method according to claim 41, wherein said chemically active area comprises an area including said biochemically active area.

43.   A method according to claim 41, wherein said chemically active area comprises a control area of said protein.

44.   A method according to claim 1, analyzing comprises analyzing successful binding of at least 60 gauges.

45.   A method according to claim 1, analyzing comprises analyzing successful binding of at least 10 gauges.

46.   A method according to claim 1, analyzing comprises analyzing successful binding of at least 100 gauges.

47.   A method according to claim 5, wherein identifying comprises identifying at least 40 different configurations.

48.   A method according to claim 5, wherein identifying comprises identifying at least 10 different configurations.

49.   A method according to claim 5, wherein identifying comprises identifying at least 100 different configurations.

50.   A method according to claim 16, comprising:
       comparing said map to a lead data base; and
       selecting a lead from said data base for further use responsive to a semblance or lack of semblance between said lead and said map.

51.   A method according to claim 16, comprising:

comparing said map to a lead data base; and

rejecting a lead from said data base for further use responsive to a semblance between said lead and said map.

5 52.   A method according to claim 16, comprising:

constructing a lead to have a semblance to said map.

53.   A method according to claim 52, wherein constructing comprises constructing using said gauges or scaffolds used to define said gauges.

10

54.   A method according to claim 5, comprising:

comparing said configurations to a lead data base; and

selecting a lead from said data base for further use responsive to a matching of said configurations to said lead.

15

55.   A method according to claim 5, comprising:

constructing a lead based on said configurations.

56.   A method according to claim 5, comprising:

20   selecting at least one of said gauges as a lead for drug discovery.

57.   A method according to claim 1, comprising comparing the binding of gauges with similar binding geometries to obtain steric clashing data; and

analyzing said steric clashing data to provide geometrical information about said target.

25

58.   A method of identifying the existence of a plurality of chemical-spatial configurations in a target, comprising:

assaying the target with a plurality of gauges having know chemical-spatial configurations at vertexes thereof, to provide a plurality of assay results;

30   defining an array of spaces, one space for each set of chemical behaviors of the vertexes of each configuration;

indicating said results according to said spaces, to generate clusters; and

identifying the existence of a configuration in said target from said clusters.

59.   A method according to claim 58, wherein indicating comprises spreading an indication responsive to a spreading function.

5   60.   A method according to claim 59, wherein said spreading function is dependent on an estimated energy of binding of a gauge to said target.

61.   A method of reconstructing a spatial shape of a chemical binding configuration of a target from a set of sub-shapes, each of which indicates a part of said binding configuration,

10   comprising:

selecting a base from said sub-shapes;

selecting at least two sub-shapes having the property that they match each other at least along one side thereof and match said base along another side thereof;

accumulating said sub-shapes to said base; and

15   repeating said selecting and said accumulating until all of said sub-shapes are used or cannot be used, thereby providing a shape of a binding configuration of said target.

62.   A method according to claim 61, comprising variationally repeating said selecting, accumulating and repeating using a different order of selection of sub-shapes.

20

63.   A method according to claim 62, comprising repeating said selecting a base and said variationally repeating for a plurality of different base selections.

64.   A method according to claim 63, comprising clustering a plurality of such shapes

25   according to shared sub-component shapes.

65.   A method according to claim 64, comprising selecting a sub-component shape as a resulting shape based on said clustering.

30   66.   A method according to claim 61, wherein said sub-shapes comprise triangles.

67. A method according to claim 61, wherein said sub-shapes define chemical behavior at their vertexes and wherein two sides are said to match if the chemical behavior at their vertexes match.

68. A method according to claim 61, wherein two sides are said to match if their length is similar.

69. A method of selecting a scaffold for use in generating a part of a screening library, comprising:

providing a potential scaffold molecule including a plurality of possible attachment points for moieties;

determining a rigidity of the molecule; and

rejecting said potential scaffold molecule responsive to a lack of rigidity of said scaffold.

70. A method according to claim 69, wherein said lack of rigidity is absolute.

71. A method according to claim 69, wherein said lack of rigidity is relative to other potential scaffolds.

72. A method according to claim 69, comprising selecting a scaffold based on a number of rings thereof.

73. A method according to claim 69, comprising:

determining a plurality of gauge molecules that can be generated by adding moieties to said potential scaffold molecule;

determining for an existing library portion what spatial chemical configurations are added by said molecules; and

selecting said potential scaffold molecule if one or more significant spatial chemical configurations can be added by it to said library portion.

74. A method according to claim 73, comprising selecting a scaffold based on a number of configurations added by said scaffold.

75. A method according to claim 73, wherein said significant spatial configurations are configurations not previously provided or overlapped with,

5   76. A method of selecting a gauge molecule to be added to a screening library, comprising:

providing a set of chemical molecules and at least a part of a screening library;

selecting a potential gauge molecule from said set of chemical molecules;

determining a rigidity of said potential gauge molecule; and

rejecting said potential gauge molecule responsive to a lack of rigidity of said gauge

10 molecule.

77. A method according to claim 76, wherein said lack of rigidity is absolute.

78. A method according to claim 76, wherein said lack of rigidity is relative to other

15 potential scaffolds.

79. A method according to claim 76, comprising:

determining a spanning, in chemical configuration space, of said part of a screening library;

20   determining at least one spatial chemical configuration of said potential molecule; and

selecting said potential gauge molecule if it adds at least one significant spatial chemical configuration to said screening library.

80. A method according to claim 76, wherein providing a set of molecules comprises

25 generating said molecules using a single scaffold to which moieties are selectively attached.

81. A method according to claim 76, wherein providing a set of molecules comprises providing a chemical library.

30 82. A method according to claim 79, wherein said gauge is selected if it adds at least one spatial chemical configuration not previously provided or overlapping a provided configuration.

83. A method of creating at least a portion of a screening library, comprising:

selecting a scaffold molecule to which moieties can be added;

determining a plurality of potential gauges which can be created by attaching moieties to said scaffold; and

selecting a subset of said gauges that do not substantially overlap in chemical configurations.

84. A method according to claim 83, comprising:

rejecting potential gauges that add over six spatial chemical configurations.

85. A method of reducing a screening library, comprising:

for each molecule in at least part of said library, determining substantially all the spatial chemical configurations of a certain order of binding points provided by the molecule; and

removing a plurality of molecules which add redundant spatial chemical configurations.

86. A method according to claim 85, wherein said certain order is three.

87. A method of reducing a screening library, comprising:

for each molecule in at least part of said library, calculating a binding probability of said molecules based on energetic considerations; and

removing at least some molecules whose binding probability is below a threshold value.

88. A method according to claim 87, wherein said binding probability is calculated using a formula which is inversely dependent on a flexibility of the molecule.

89. A method according to claim 87, wherein said binding probability is at least estimated based on a solubility of the molecule.

90. A method of designing a screening library for a projected target molecule task, comprising:

determining a desired range of distances between binding points to be directly identified by said library;

determining a desired overlap between measures provided by gauge molecules of said library;

5   determining a set of desired binding types to be discriminated between; and

generating a plurality of gauges, said gauges each defining a plurality of binding types and distances between them, such that said gauges cover a spatial chemical configuration space that includes said distances and said binding types with said desired overlap.

10   91.   A method according to claim 90, wherein generating a plurality of moieties comprises generating by attaching moieties to scaffolds.

92.   A method according to claim 90, wherein said gauges cover a spatial chemical configuration space of triplets of binding points.

15

93.   A method according to claim 90, wherein said projected target molecule task comprises proteins.

94.   A method according to claim 90, wherein said overlap is at least two.

20

95.   A method according to claim 90, wherein said overlap is at least four.

96.   A method according to claim 90, wherein said overlap is at least six.

25   97.   A method according to claim 90, wherein said gauges are substantially rigid.

98.   A method according to claim 90, wherein said coverage takes into account an inherent flexibility of binding.

30   99.   A method according to claim 90, wherein generating comprises generating substantially same configurations by different gauges, thereby providing at least part of said overlap.

100.   A method according to claim 99, wherein generating comprises providing a repetition factor of at least two.

101.   A method according to claim 90, wherein generating comprises generating substantially different configurations by different gauges, which different configurations overlap due to a degree of flexibility thereof, thereby providing at least part of said overlap.

102.   A method according to claim 1, comprising generating a set of drug leads for said target based on said information.

103.   A method according to claim 102, comprising removing known drug leads for said target from said set.

104.   A lead set produced by the method of claim 102.

105.   A lead set produced by the method of claim 103.

106.   A drug lead comprising:
        a plurality of substantially rigid scaffolds molecule sections;
        at least one link interconnecting said scaffold molecule sections; and
        a plurality of moieties attached to said scaffolds.

107.   A screening library comprising:
        at least 10,000 molecules generated by attaching moieties to a set of fewer than 50 scaffold molecules.

108.   A screening library according to claim 107, wherein fewer than 20 scaffold molecules are used to generate said at least 10,000 molecules.

109.   A library according to claim 107, wherein said scaffolds include at least one of the following scaffold molecules: Thiophene; 1H-Pyrrole; Furan; Benzene; Pyridine; Pyrimidine; Pyrazine;   6H-Thieno[2,3-b]pyrrole;   1,6-Dihydro-pyrrolo[2,3-b]pyrrole;   1H-Indole; Thieno[2,3-d]pyrimidine; 6,7-Dihydro-pyrazolo[1,5-a]pyrimidine; Quinoline; Isoquinoline;

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Quinoxaline; 3,4-Dihydro-benzo[e][1,4]diazepin-5-one; 3,8-Dihydro-4H-pyrrolo[2,3-e][1,4]diazepin-5-one; 3,4-Dihydro-thieno[2,3-e][1,4]diazepin-5-one; 3,6-Dihydro-4H-pyrrolo[3,2-e][1,4]diazepin-5-one; 5H,11H-Dibenzo[b,f][1,5]diazocine-6,12-dione; 1,4-Dihydro-10H-1,4,10-1,4,10-triaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione; 4H,10H-1-

5 Thia-4,10-diaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione; Dipyrrolo[1,2-c;2',1'-e]imidazol-5-one; 1,4,7,9-Tetrahydro-1,4,6,9-tetraaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 4,7,9-Trihydro-1-thia-4,6,9-triaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 2,4,9,Trihydro-1lambda*4*,6-dithia-4,9-diaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 6,9-Dihydro-5H-1-thia-5,8,9,triaza-cyclopenta[a]azulen-4-one; 3,10,Dihydro-4H-

10 [1,4]diazepino[5,6-b]indol-5-one; 3,6-Dihydro-4H-[1,4]diazepino[6,5-b]indol-5-one; 7,8-Dihydro-1H-1,7,10-triaza-cyclohepta[e]inden-6-one; 8,9-Dihydro-3H-3,6,9-triaza-cyclohepta[e]inden-10-one; 7,8-Dihydro-1H-1,5,8-triaza-cyclohepta[f]inden-9-one; 8,9-Dihydro-5,6,9,11-tetraaza-cyclohept[b]naphthalene-10-one; 3,4-Dihydro-[1,4]diazepino[5,6-b]quinolin-5-one; 8,9-Dihydro-4,8,11-triaza-cyclohepta[a]naphthalene-7-one; 11H-10,11-

15 Diaza-benzo[b]fluorine; α-hydroxyacids; α-aminoacids; cohels; Bicyclo[2.2.2]octane; 2-Methylene-2,3-dihydrobenzo[1,4]dioxine; 6,7-Dihydro-2H-pyrazino[1,2-a]pyramidine; 9H-Fluorene; 1,4-Diaza-bictclo[2.2.2]octane; 1-Aza-bicyclo[2.2.2]octane; Pyrido[2,3-d]pyrimidine; 5-Methylene-1,5-dihydro-pyrrol-2-one; Bezno[4,5]imidazo[1,2-a]pyrimidine; 1,4-Dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine; 4,10-Dihydro-1,4a,10-triaza-phenanthren-9-

20 one; 1,5-Dihydro-imidazo[1,2-a]pyrimidin-2-one; 1,2,3,5-Tetrahydro-imidazo[1,2-a]pyrimidine; Thiazolo[3,2-a]thieno[2,3-d]pyrimidin-5-one; 1,9-Dithia-4a,10-diaza-cyclopenta[b]fluoren-4-one; 5,6-Dihydro-1-thia-5,7,8,9a-tetraaza-cyclopenta[e]azulen-4-one; 6,10-Dihydro-5H-1-thia-5,7,10a-triaza-benzo[e]azulen-4-one; 4,5-Dihydro-3-thia-4,5a,10-triaza-cyclopenta[a]fluorine; 8H-1-Thia-cyclopenta[a]indene; 3-Thia-4,5a,10-triaza-

25 cyclopenta[a]fluorine; 6,7,9,11-Tetrahydro-10-thia-6,9-diaza-indeno[1,2-a]azulene-5,8-dione; 2,3,6,7,12a-Hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione; 5,10-Dihydro-4H-2,3a,10-triaza-cyclopenta[a]fluorine; 5H-Pyrido[4,3-b]indole; 11H-Indolizino[1,2-b]quinolin-9-one; 1,2-Dihydro-2,4a,9,-triaza-anthracene-3,10-dione; 6H-Isoindolo[2,1-a]indole; 1,5-Dihydro-benzo[b][1,4]diazepin-2-one; 5,10-Dihydro-dibenzo[b,e][1,4]diazepin-11-one; 5,11-

30 Dihydro-benzo[e]pyrido[3,2-b][1,4]diazepin-6-one; 4,9-Dihydro-3-thia-4,9-diaza-benzo[f]azulen-10-one; Benzo[g]quinoxaline; Pyrazino[2,3-b]quinoxaline; Pyrido[2,1-b]quinazolin-11-one; 1-Thia-4a,9-diaza-cyclopenta[b]naphthalene-4-one; 2-Methylene-4H-benzo[1,4]thiazin-3-one.

110.   A library according to claim 107, wherein at least 4 of said scaffolds have exactly a single ring.

5   111.   A library according to claim 107, wherein at least 4 of said scaffolds have exactly two rings.

112.   A library according to claim 107, wherein at least 4 of said scaffolds have exactly three rings.

10

113.   A library according to claim 107, wherein at least 4 of said scaffolds have exactly four rings.

114.   A library according to claim 107, wherein said library includes at least 50,000 thus

15   generated molecules.

115.   A library according to claim 107, wherein said library includes at least 100,000 thus generated molecules.

20   116.   A library according to claim 109, wherein said scaffolds include at least three of said following scaffold molecules.

117.   A library according to claim 109, wherein said scaffolds include at least ten of said following scaffold molecules.

25

118.   A library according to claim 107, wherein said generated molecules are substantially rigid.

119.   A library according to claim 107, wherein said molecules span a configuration space of

30   spatial geometrical patterns of binding point types, including at least 25% of the patterns that exist in protein targets.

120.   A library according to claim 119, wherein said molecules span at least 50% of the patterns.

121.   A library according to claim 119, wherein said molecules span a space defining at least

5   4 distinct binding point chemistry types.

122.   A library according to claim 119, wherein said molecules span a space defining at least 5 distinct binding point chemistry types.

10   123.   A screening library, comprising:

at least 100 gauge molecules generated by attaching moieties to at least one of the following scaffolds: Thiophene; 1H-Pyrrole; Furan; Benzene; Pyridine; Pyrimidine; Pyrazine; 6H-Thieno[2,3-b]pyrrole; 1,6-Dihydro-pyrrolo[2,3-b]pyrrole; 1H-Indole; Thieno[2,3-d]pyrimidine; 6,7-Dihydro-pyrazolo[1,5-a]pyrimidine; Quinoline; Isoquinoline; Quinoxaline;

15   3,4-Dihydro-benzo[e][1,4]diazepin-5-one; 3,8-Dihydro-4H-pyrrolo[2,3-e][1,4]diazepin-5-one; 3,4-Dihydro-thieno[2,3-e][1,4]diazepin-5-one; 3,6-Dihydro-4H-pyrrolo[3,2-e][1,4]diazepin-5-one; 5H,11H-Dibenzo[b,f][1,5]diazocine-6,12-dione; 1,4-Dihydro-10H-1,4,10-1,4,10-triaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione;   4H,10H-1-Thia-4,10-diaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione;   Dipyrrolo[1,2-c;2',1'-e]imidazol-5-one;

20   1,4,7,9-Tetrahydro-1,4,6,9-tetraaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 4,7,9-Trihydro-1-thia-4,6,9-triaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 2,4,9,Trihydro-11lambda*4*,6-dithia-4,9-diaza-dicyclopenta[a,e]cyclooctene-5,10-dione; 6,9-Dihydro-5H-1-thia-5,8,9,triaza-cyclopenta[a]azulen-4-one; 3,10,Dihydro-4H-[1,4]diazepino[5,6-b]indol-5-one; 3,6-Dihydro-4H-[1,4]diazepino[6,5-b]indol-5-one; 7,8-Dihydro-1H-1,7,10-triaza-cyclohepta[e]inden-6-one;

25   8,9-Dihydro-3H-3,6,9-triaza-cyclohepta[e]inden-10-one;   7,8-Dihydro-1H-1,5,8-triaza-cyclohepta[f]inden-9-one; 8,9-Dihydro-5,6,9,11-tetraaza-cyclohept[b]naphthalene-10-one; 3,4-Dihydro-[1,4]diazepino[5,6-b]quinolin-5-one;   8,9-Dihydro-4,8,11-triaza-cyclohepta[a]naphthalene-7-one; 11H-10,11-Diaza-benzo[b]fluorine; α-hydroxyacids; α-aminoacids; cohels; Bicyclo[2.2.2]octane; 2-Methylene-2,3-dihydrobenzo[1,4]dioxine; 6,7-

30   Dihydro-2H-pyrazino[1,2-a]pyramidine; 9H-Fluorene; 1,4-Diaza-bictclo[2.2.2]octane; 1-Aza-bicyclo[2.2.2]octane;   Pyrido[2,3-d]pyrimidine;   5-Methylene-1,5-dihydro-pyrrol-2-one; Bezno[4,5]imidazo[1,2-a]pyrimidine; 1,4-Dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine; 4,10-Dihydro-1,4a,10-triaza-phenanthren-9-one;   1,5-Dihydro-imidazo[1,2-a]pyrimidin-2-one;

1,2,3,5-Tetrahydro-imidazo[1,2-a]pyrimidine; Thiazolo[3,2-a]thieno[2,3-d]pyrimidin-5-one; 1,9-Dithia-4a,10-diaza-cyclopenta[b]fluoren-4-one; 5,6-Dihydro-1-thia-5,7,8,9a-tetraaza-cyclopenta[e]azulen-4-one; 6,10-Dihydro-5H-1-thia-5,7,10a-triaza-benzo[e]azulen-4-one; 4,5-Dihydro-3-thia-4,5a,10-triaza-cyclopenta[a]fluorine; 8H-1-Thia-cyclopenta[a]indene; 3-Thia-4,5a,10-triaza-cyclopenta[a]fluorine; 6,7,9,11-Tetrahydro-10-thia-6,9-diaza-indeno[1,2-a]azulene-5,8-dione; 2,3,6,7,12a-Hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione; 5,10-Dihydro-4H-2,3a,10-triaza-cyclopenta[a]fluorine; 5H-Pyrido[4,3-b]indole; 11H-Indolizino[1,2-b]quinolin-9-one; 1,2-Dihydro-2,4a,9,-triaza-anthracene-3,10-dione; 6H-Isoindolo[2,1-a]indole; 1,5-Dihydro-benzo[b][1,4]diazepin-2-one; 5,10-Dihydro-dibenzo[b,e][1,4]diazepin-11-one; 5,11-Dihydro-benzo[e]pyrido[3,2-b][1,4]diazepin-6-one; 4,9-Dihydro-3-thia-4,9-diaza-benzo[f]azulen-10-one; Benzo[g]quinoxaline; Pyrazino[2,3-b]quinoxaline; Pyrido[2,1-b]quinazolin-11-one; 1-Thia-4a,9-diaza-cyclopenta[b]naphthalene-4-one; 2-Methylene-4H-benzo[1,4]thiazin-3-one.

124. A library according to claim 123, wherein said molecules are generated using at least one of the following scaffolds:

Thiophene; 1H-Pyrrole; Furan; Benzene; Pyridine; Pyrimidine; Pyrazine; 6H-Thieno[2,3-b]pyrrole; 1,6-Dihydro-pyrrolo[2,3-b]pyrrole; 1H-Indole; Thieno[2,3-d]pyrimidine; 6,7-Dihydro-pyrazolo[1,5-a]pyrimidine; Quinoline; Isoquinoline; Quinoxaline; 3,4-Dihydro-benzo[e][1,4]diazepin-5-one; 3,8-Dihydro-4H-pyrrolo[2,3-e][1,4]diazepin-5-one; 3,4-Dihydro-thieno[2,3-e][1,4]diazepin-5-one; 3,6-Dihydro-4H-pyrrolo[3,2-e][1,4]diazepin-5-one; 5H,11H-Dibenzo[b,f][1,5]diazocine-6,12-dione; 1,4-Dihydro-10H-1,4,10-1,4,10-triaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione; 4H,10H-1-Thia-4,10-diaza-benzo[a]cyclopenta[e]cyclooctene-5,11-dione; Dipyrrolo[1,2-c;2',1'-e]imidazol-5-one.

125. A library according to claim 123, wherein said at least 100 molecules comprise at least 300 molecules.

126. A library according to claim 123, wherein said at least 100 molecules of said library are generated using a single one of said scaffolds.

127. A screening library comprising a set of at least 10,000 substantially rigid molecules.

128.   A library according to claim 127, wherein said set comprises at least 50,000 substantially rigid molecules.

129.   A library according to claim 127, wherein said set comprises at least 100,000 substantially rigid molecules.

130.   A library according to claim 127, wherein said set is selected to have a an expected binding rate of at least 0.1% of the library for protein targets in general.

131.   A library according to claim 130, wherein said expected binding rate is at least 0.5%.

132.   A library according to claim 130, wherein said set is designed to provide molecules with a uniformity of hit probability for a generalized target of within a ratio of 1:100 for the whole set.

133.   A library according to claim 132, wherein said ratio is within 1:10.

134.   A library according to claim 127, wherein said set spans a space of spatial chemical configurations, each such configuration defining a certain plurality of binding points having distances between them, the set covering substantially all possible configurations in the space in a given range of distances.

135.   A screening library, comprising:

        a plurality of at least 5,000 gauge molecules, each such molecule defining at least one spatial configuration of binding type points,

        wherein substantially each point in a space of such configurations is covered by at least two different gauge molecules.

136.   A library according to claim 135, wherein each point is covered by at least two substantially identical spatial configurations.

137.   A library according to claim 135, wherein each point is covered by at least two substantially different spatial configurations.

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138.   A library according to claim 135, wherein said space is a space of triangles defined by binding type at vertexes and distances between vertexes.

139.   A library according to claim 138, wherein said space includes distances of between 4 Å and 8 Å (angstrom $= 10^{-10}$ meters).

140.   A library according to claim 138, wherein said space includes distances of between 2 Å and 10 Å.

141.   A library according to claim 138, wherein said space includes at least 5 different binding types.

142.   A library according to claim 138, wherein said space includes at least 7 different binding types.

143.   A library according to claim 138, wherein said space includes omni-directional binding types.

144.   A library according to claim 138, wherein said space includes directional binding types.

145.   A library according to claim 138, wherein said substantially each point in said space is covered by at least three gauges.

146.   A library according to claim 138, wherein substantially all the gauges include a plurality of configurations of said space.

147.   A method of obtaining information about a binding behavior of a target molecule, comprising:
        providing a set of substantially rigid chemical gauges, a significant number of said gauges being expected to bind with said target;
        reacting said target with a plurality of gauges of said set of gauges; and
        physically analyzing a structure of said target bound to a gauge.

148. A method according to claim 147, wherein physically analyzing comprises analyzing using NMR.

5   149. A method according to claim 147, wherein physically analyzing comprises analyzing using X-ray crystallography.

150. A method according to claim 147, wherein physically analyzing comprises analyzing using binding with a set of gauges.

10

151. A method according to claim 147, comprising virtually super-imposing a plurality of structures obtained by said physically analyzing.

152. A method of constructing a lead, comprising:

15   providing a set of substantially rigid chemical gauges;

reacting said target with a plurality of gauges of said set of gauges;

assaying a binding of said gauges with said target to obtain a plurality of assay results; and

constructing a lead based on said assay results.

20

153. A method according to claim 152, wherein constructing a lead comprises linking together a plurality of gauges found to bind in said assaying.

154. A method according to claim 152, wherein constructing a lead comprises modifying an

25   existing molecule to have moieties that correspond to binding locations found by said assaying.

FIG.1

2/5

PROVIDE
TARGET ⟞ 202

↓

SELECT
GAUGES ⟞ 204

↓

MEASURE
TARGET ⟞ 206

↓

RECONSTRUCT
TARGET ⟞ 208

↓

FWD MATCH
TO TARGET ⟞ 210

↓

TEST MATCH
SUITABILITY ⟞ 212

↓

FINE TUNE ⟞ 214

200

FIG.2

COMBINE GAUGE
AND TARGET ⟞ 302

↓

INCUBATE ⟞ 304

↓

ASSAY
BINDING ⟞ 306

↓

ASSAY TARGET
ACTIVITY ⟞ 308

↓

CHANGE
CONDITIONS ⟞ 310

300

FIG.3

FIG.4A

FIG.4B

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DEFINE A SPACE FOR
EACH TRIANGLE TYPE ⟋502   500

↓

MARK ESSAY RESULTS
IN RELEVANT SPACE(S) ⟋504

↓

SPREAD HIT MARKS ⟋506

↓

THRESHOLD PEAKS ⟋508

FIG.5

CONSTRUCT ALL
LEGAL STRUCTURES ⟋602   600

↓

CALCULATE SCORES
FOR STRUCTURES ⟋604

↓

SELECT STRUCTURE
WITH HIGHEST SCORE ⟋606

FIG.6A

5/5

```
                    ┌──────────────────────────┐
                    │    SELECT  TRIANGLE       │──── 622          620
                    │    AS  BASE  STRUCTURE    │
                    └──────────────────────────┘
                                │
                                ▼
                    ┌──────────────────────────┐
                    │      FIND  TWO            │──── 624
                    │   TRIANGLES  TO  ADD      │
                    └──────────────────────────┘
                                │
                                ▼
                    ┌──────────────────────────┐
                    │    IF  CAN  STILL  ADD    │──── 626
                    │     TWO  TRIANGLES        │
                    └──────────────────────────┘
                                │
                                ▼
                    ┌──────────────────────────────┐
                    │  REPEAT  WITH  ALL  OTHER     │──── 628
                    │ SELECTIONS  OF  TRIANGLE PAIRS│
                    └──────────────────────────────┘
                                │
                                ▼
                    ┌──────────────────────────┐
                    │  REPEAT  WITH  ALL  OTHER │──── 630
                    │   TRIANGLES  AS  BASES    │
                    └──────────────────────────┘
                                │
                                ▼
                    ┌──────────────────────────┐
                    │   FIND  ALL  COMMON       │──── 632
                    │    SUBSTRUCTURES          │
                    └──────────────────────────┘
                                │
                                ▼
                    ┌──────────────────────────┐
                    │   CLUSTER  COMMON         │──── 634
                    │    SUBSTRUCTURES          │
                    └──────────────────────────┘
                                │
                                ▼
                    ┌──────────────────────────┐
                    │    SELECT  BEST           │──── 636
                    │   SUBSTRUCTURE(S)         │
                    └──────────────────────────┘
```

FIG.6B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL02/00614

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01N 31/00, 33/48; G06F 19/00
US CL : 702/19,22,27

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 702/19,22,27

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN on line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	FEJZO et al. The SHAPES strategy: an NMR-based approach for lead generation in drug discovery. Chemistry & Biology, October 1999, Vol. 6, No. 10, pages 755-769. See abstract.	1-7,36,41-43,57,102,103 ----------- 14,15,24-35,44-46
X --- Y	SANNES-LOWERY et al. High-performance mass spectrometry as a drug discovery tool: a high-throughput screening assay to identify RNA-binding ligands. Proceedings of SPIE-The International Society for Optical Engineering (2001), Vol. 4264, pages 27-36. See abstract.	1-7,36,41-43,57,102,103 ----------- 14,15,24-35,44-46
Y	DARVAS, F. et al. A Photoactivatable Library Approach for Target Identificaion and Validation. Publisher: American Chemical Society, Washington, D.C., April 2002, see abstract #MEDI-245.	1-7,14,15,24-36,41-46,57,102,103
A	WO 98/16835 A2 (TERRAPIN TECHNOLOGIES, INC.) 23 April 1998 (23.04.1998), entire document.	36,41-46,57,102,103

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier application or patent published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed

"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 July 2003 (08.07.2003)	**19 AUG 2003**

Name and mailing address of the ISA/US	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	(Michael Borin)
Facsimile No. (703)305-3230	Telephone No. 703-308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL02/00614

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-7,14,15,24-36,41-46,57,102,103

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1)) (July 1998)

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group 1, claims 1-57, 102, 103, drawn to methods of obtaining information about active area of a target molecule.

Group II, claims 58-60, drawn to method of identifying existence of plurality of chemical-spatial configurations in a target molecule.

Group III, claims 61-68, drawn to method of reconstructing spatial shape of chemical binding configuration.

Group IV, claims 69-75, drawn to method for selecting a scaffold.

Group V, claims 76-82, drawn to method for selecting a gauge molecule.

Group VII, claims 85-89, drawn to method for reducing screening library.

Group VIII, claims 90-101, drawn to method for designing a screening library.

Group IX, claims 104, 105, drawn to lead set.

Group X, claims 106, drawn to a drug lead.

Group XI, claims 107-126, drawn to first screening library comprising at least 10,000 molecules derived from scaffold molecules.

Group XII, claims 127-134, drawn to second screening library comprising rigid molecules.

Group XIII, claims 135-146, drawn to third screening library comprising gauge molecules.

Group XIV, claims 147-151, drawn to method of obtaining information.

Group XV, claims 152-154, drawn to method of constructing a lead.

In addition, Group I of this application contains claims directed to more than one species of the generic invention. The species identified below are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be examined, the appropriate additional search fees must be paid. The species are as follows:

A.   For claims 7-13, 5 species of "identifying", such as identifying configuration that matches configuration of a bound gauge, does not match configuration of a bound gauge, identifying by statistical analysis, by clustering, etc.

B.   For claims 14-16, 2 species of "reconstructing", such as based on assay results, or based on configurations.

C.   For claims 18, 19 - 2 species of reconstruction steps, such as based on scoring maps, or on maps clustering.

D.   For claims 36-39 - 4 species of assay types, such as functional, binding, cellular, flow-through.

E.   For claims 50-52 - 3 species of utilizing lead in map analysis: selecting a lead, rejecting a lead, constructing a lead. The inventions listed as Groups I-VIII, Xiv, Xv do not related to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Each of the Groups claim a distinct and separate method. The methods do not share a special technical feature because each method contains specific and unique method steps which are not shared by each of the other methods and each method has a unique and distinct outcome. Thus, group I-VIII, XIV, XV do not share a corresponding special technical feature.

The inventions listed as Groups IX-XII do not relate to a single general inventive concept under PCT rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features: the libraries are produced by different methods, and there is no common core structure identified for said libraries of compounds.

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(54) Title: ORGANIC LIGHT EMITTING MATERIALS WITH ANIONIC LIGAND

(57) Abstract: Emissive phosphorescent organometallic compounds that produce electroluminescence and organic light emitting devices employing such emissive phosphorescent organometallic compounds are provided. More specifically the present invention is directed to novel primarily non-emitting ligands which produce a blue shift in emitted light when associated with a cyclometallated ligand.

ORGANIC LIGHT EMITTING MATERIALS WITH ANIONIC
LIGAND

[0001]   This application is related to and claims priority from U.S. Provisional Patent

5   Application 60/404,087, filed August 16, 2002, which is incorporated herein in its entirety.

Field of the Invention

[0002]   The present invention is directed to phosphorescence based organic light

emitting materials and devices that have improved electroluminescent characteristics. More

10   specifically, the present invention relates to materials and devices that are, for example,

capable of emitting in the blue region of the visible spectrum.

Background

[0003]   Opto-electronic devices that make use of organic materials are becoming

15   increasingly desirable for a number of reasons. Many of the materials used to make such

devices are relatively inexpensive. Consequently, organic opto-electronic devices have the

potential for cost advantages over inorganic devices. In addition, the inherent properties of

organic materials, such as their flexibility, may make them well suited for particular

applications such as fabrication on a flexible substrate. Examples of organic opto-electronic

20   devices include organic light emitting devices (OLEDs), organic phototransistors, organic

photovoltaic cells, and organic photodetectors. For OLEDs, the organic materials may have

performance advantages over conventional materials. For example, the wavelength at which

an organic emissive layer emits light may generally be readily tuned with appropriate

dopants.

25   [0004]   As used herein, the term "organic" includes polymeric materials as well as

small molecule organic materials that may be used to fabricate organic opto-electronic

devices. "Small molecule" refers to any organic material that is not a polymer, and "small

molecules" may actually be quite large. Small molecules may include repeat units in some

circumstances. For example, using a long chain alkyl group as a substituent does not remove a molecule from the "small molecule" class. Small molecules may also be incorporated into polymers, for example as a pendent group on a polymer backbone or as a part of the backbone. Small molecules may also serve as the core moiety of a dendrimer, which consists

5   of a series of chemical shells built on the core moiety. The core moiety of a dendrimer may be an fluorescent or phosphorescent small molecule emitter. A dendrimer may be a "small molecule," and it is believed that all dendrimers currently used in the field of OLEDs are small molecules.

        [0005]   OLEDs make use of thin organic films that emit light when voltage is applied

10   across the device. OLEDs are becoming an increasingly interesting technology for use in applications such as flat panel displays, illumination, and backlighting. Several OLED materials and configurations are described in U.S. Patent Nos. 5,844,363, 6,303,238, and 5,707,745, which are incorporated herein by reference in their entirety.

        [0006]   OLED devices are generally (but not always) intended to emit light through at

15   least one of the electrodes, and one or more transparent electrodes may be useful in an organic opto-electronic device. For example, a transparent electrode material, such as indium tin oxide (ITO), may be used as the bottom electrode. A transparent top electrode, such as disclosed in U.S. Patent Nos. 5,703,436 and 5,707,745, which are incorporated by reference in their entireties, may also be used. For a device intended to emit light only through the

20   bottom electrode, the top electrode does not need to be transparent, and may be comprised of a thick and reflective metal layer having a high electrical conductivity. Similarly, for a device intended to emit light only through the top electrode, the bottom electrode may be opaque and / or reflective. Where an electrode does not need to be transparent, using a thicker layer may provide better conductivity, and using a reflective electrode may increase

25   the amount of light emitted through the other electrode, by reflecting light back towards the transparent electrode. Fully transparent devices may also be fabricated, where both electrodes are transparent. Side emitting OLEDs may also be fabricated, and one or both electrodes may be opaque or reflective in such devices.

        [0007]   As used herein, "top" means furthest away from the substrate, while "bottom"

30   means closest to the substrate. For example, in a device having two electrodes, the bottom

electrode is the electrode closest to the substrate, and is generally the first electrode fabricated. The bottom electrode has two surfaces, a bottom surface closest to the substrate, and a top surface further away from the substrate. Where a first layer is described as "disposed over" a second layer, the first layer is disposed further away from substrate. There

5   may be other layers between the first and second layer, unless it is specified that the first layer is "in physical contact with" the second layer. For example, a cathode may be described as "disposed over" an anode, even though there are various organic layers in between.

[0008]   The technology of organic light emitting diodes (OLEDs) is undergoing rapid

10   development. OLEDs originally utilized the electroluminescence produced from electrically excited molecules that emitted light from their singlet states as disclosed, for example, in U.S. Patent No. 4,769,292. Such radiative emission from a singlet excited state is referred to as fluorescence. More recent work has demonstrated that higher power efficiency OLEDs can be made using molecules that emit light from their triplet state, defined as phosphorescence.

15   Such electrophosphorescence makes it possible for phosphorescent OLEDs to have substantially higher quantum efficiencies than are possible for OLEDs that only produce fluorescence. This is based on the understanding that the excitons created in an OLED are produced, according to simple statistical arguments as well as experimental measurements, approximately 75% as triplet excitons and 25% as singlet excitons. The triplet excitons more

20   readily transfer their energy to triplet excited states that can produce phosphorescence whereas the singlet excitons typically transfer their energy to singlet excited states that can produce fluorescence.

[0009]   Since the lowest emissive singlet excited state of an organic molecule is typically at a slightly higher energy than the lowest triplet excited state, the singlet excited

25   state may relax, by an intersystem crossing process, to the emissive triplet excited state. This means that all the exciton excitation energy may be converted into triplet state excitation energy, which then becomes available as phosphorescent emission. Thus, electrophosphorescent OLEDs have a theoretical quantum efficiency of 100%, since all the excitation energy can become available as electrophosphorescence.

30   [00010]   In contrast, only a small percentage (about 25%) of excitons in fluorescent

devices are capable of producing the fluorescent luminescence that is obtained from a singlet excited state. The remaining excitons in a fluorescent device, which are produced in the lowest triplet excited state of an organic molecule, are typically not capable of being converted into the energetically unfavorable higher singlet excited states from which the

5   fluorescence is produced. This energy, thus, becomes lost to radiationless decay processes that heat-up the device.

[00011]   As a consequence, since the discovery that phosphorescent materials could be used in an OLED, Baldo et al., *"Highly Efficient Phosphorescent Emission from Organic Electroluminescent Devices", Nature, vol. 395, 151-154, 1998,* there is now much interest in

10   finding more efficient electrophosphorescent materials. OLEDs utilizing phosphorescent materials are disclosed, for example, in U.S. Patent No. 6,303,238 which is incorporated by reference in its entirety.

[00012]   Typically, phosphorescent emission from organic molecules is less common than fluorescent emission. However, phosphorescence can be observed from organic

15   molecules under an appropriate set of conditions. It would be desirable if more efficient electrophosphorescent materials could be found, particularly materials that produce their emission in the technologically useful blue and green colors of the visible spectrum.

SUMMARY OF THE INVENTION

20   [00013]   The present invention is directed to emissive phosphorescent organometallic compounds that produce improved electroluminescence, organic light emitting devices employing such emissive phosphorescent organometallic compounds. More specifically the present invention is directed to novel primarily non-emitting ligands which produce a blue shift in emitted light when associated with a cyclometallated ligand.

25   [00014]   Specific embodiments of the present invention are directed to OLEDs using emissive phosphorescent organometallic compounds that produce improved electrophosphorescence in the blue region of the visible spectrum.

BRIEF DESCRIPTION OF THE DRAWINGS

[00015]   Figure 1 shows an organic light emitting device having separate electron transport, hole transport, and emissive layers, as well as other layers.

[00016]   Figure 2 shows an inverted organic light emitting device that does not have a separate electron transport layer.

5

DESCRIPTION OF THE INVENTION

[00017]   The present invention will now be described in detail for specific preferred embodiments of the invention. These embodiments are intended to be illustrative and the invention is not limited in scope to the specific preferred embodiments described.

10

[00018]   The present invention relates to OLEDs that efficiently emit light, in particular, that preferably emit light in the blue range of the visible spectrum, and to the phosphorescent emissive materials used in the devices. The invention also relates to non-emitting ligands that produce a hypsochromic (blue) shift in the emission spectrum of light

15   emitted by an associated emitting ligand.

[00019]   Generally, an OLED comprises at least one organic layer disposed between and electrically connected to an anode and a cathode. When a current is applied, the anode injects holes and the cathode injects electrons into the organic layer(s). The injected holes

20   and electrons each migrate toward the oppositely charged electrode. When an electron and hole localize on the same molecule, an "exciton," which is a localized electron-hole pair having an excited energy state, is formed. Light is emitted when the exciton relaxes via a photoemissive mechanism. In some cases, the exciton may be localized on an excimer or an exciplex. Non-radiative mechanisms, such as thermal relaxation, may also occur, but are

25   generally considered undesirable.

[00020]   The initial OLEDs used emissive molecules that emitted light from their singlet states ("fluorescence") as disclosed, for example, in U.S. Patent No. 4,769,292, which is incorporated by reference in its entirety. Fluorescent emission generally occurs in a time

30   frame of less than 10 nanoseconds.

[00021]   More recently, OLEDs having emissive materials that emit light from triplet
states ("phosphorescence") have been demonstrated. Baldo et al., "Highly Efficient
Phosphorescent Emission from Organic Electroluminescent Devices," Nature, vol. 395, 151
154, 1998; ("Baldo I") and Baldo et al., "Very high efficiency green organic light emitting
devices based on electrophosphorescence," Appl. Phys. Lett., vol. 75, No. 3, 4 6 (1999)
("Baldo II"), which are incorporated by reference in their entireties. Phosphorescence may
be referred to as a "forbidden" transition because the transition requires a change in spin
states, and quantum mechanics indicates that such a transition is not favored. As a result,
phosphorescence generally occurs in a time frame exceeding at least 10 nanoseconds, and
typically greater than 100 nanoseconds. If the natural radiative lifetime of phosphorescence
is too long, triplets may decay by a non-radiative mechanism, such that no light is emitted.
Organic phosphorescence is also often observed in molecules containing heteroatoms with
unshared pairs of electrons at very low temperatures. 2,2' bipyridine is such a molecule.
Non-radiative decay mechanisms are typically temperature dependent, such that a material
that exhibits phosphorescence at liquid nitrogen temperatures may not exhibit
phosphorescence at room temperature. But, as demonstrated by Baldo, this problem may be
addressed by selecting phosphorescent compounds that do phosphoresce at room
temperature.

[00022]   Generally, the excitons in an OLED are believed to be created in a ratio of
about 3:1, i.e., approximately 75% triplets and 25% singlets. See, Adachi et al., "Nearly
100% Internal Phosphorescent Efficiency In An Organic Light Emitting Device," J. Appl.
Phys., 90, 5048 (2001), which is incorporated by reference in its entirety. In many cases,
singlet excitons may readily transfer their energy to triplet excited states via "intersystem
crossing," whereas triplet excitons may not readily transfer their energy to singlet excited
states. As a result, 100% internal quantum efficiency is theoretically possible with
phosphorescent OLEDs. In a fluorescent device, the energy of triplet excitons is generally
lost to radiationless decay processes that heat up the device, resulting in much lower internal
quantum efficiencies. OLEDs utilizing phosphorescent materials that emit from triplet
excited states are disclosed, for example, in U.S. Patent No. 6,303,238, which is incorporated
by reference in its entirety.

[00023]   Phosphorescence may be preceded by a transition from a triplet excited state
to an intermediate non-triplet state from which the emissive decay occurs. For example,
organic molecules coordinated to lanthanide elements often phosphoresce from excited states
5   localized on the lanthanide metal. However, such materials do not phosphoresce directly
from a triplet excited state but instead emit from an atomic excited state centered on the
lanthanide metal ion. The europium diketonate complexes illustrate one group of these types
of species.

10   [00024]   Phosphorescence from triplets can be enhanced over fluorescence by
confining, preferably through bonding, the organic molecule in close proximity to an atom of
high atomic number. This phenomenon, called the heavy atom effect, is created by a
mechanism known as spin orbit coupling. Such a phosphorescent transition may be observed
from an excited metal to ligand charge transfer (MLCT) state of an organometallic molecule
15   such as tris(2 phenylpyridine)iridium(III). Molecules that phosphoresce from MLCT triplet
states, However, typically emit light that is of lower energy than that observed from the
unbound organic ligand. This lowering of emission energy presents a challenge in the
development of organic molecules that phosphoresce in the technologically useful blue and
green colors of the visible spectrum where the unperturbed phosphorescence typically occurs.
20

[00025]   Figure 1 shows an organic light emitting device 100. The figures are not
necessarily drawn to scale. Device 100 may include a substrate 110, an anode 115, a hole
injection layer 120, a hole transport layer 125, an electron blocking layer 130, an emissive
layer 135, a hole blocking layer 140, an electron transport layer 145, an electron injection
25   layer 150, a protective layer 155, and a cathode 160. Cathode 160 is a compound cathode
having a first conductive layer 162 and a second conductive layer 164. Device 100 may be
fabricated by depositing the layers described, in order.

[00026]   Substrate 110 may be any suitable substrate that provides desired structural
30   properties. Substrate 110 may be flexible or rigid. Substrate 110 may be transparent,
translucent or opaque. Plastic and glass are examples of preferred rigid substrate materials.
Plastic and metal foils are examples of preferred flexible substrate materials. Substrate 110

may be a semiconductor material in order to facilitate the fabrication of circuitry. For example, substrate 110 may be a silicon wafer upon which circuits are fabricated, capable of controlling OLEDs subsequently deposited on the substrate. Other substrates may be used. The material and thickness of substrate 110 may be chosen to obtain desired structural and optical properties.

[00027]   Anode 115 may be any suitable anode that is sufficiently conductive to transport holes to the organic layers. The material of anode 115 preferably has a work function higher than about 4 eV (a "high work function material"). Preferred anode materials include conductive metal oxides, such as indium tin oxide (ITO) and indium zinc oxide (IZO), aluminum zinc oxide (AlZnO), and metals. Anode 115 (and substrate 110) may be sufficiently transparent to create a bottom-emitting device. A preferred transparent substrate and anode combination is commercially available ITO (anode) deposited on glass or plastic (substrate). A flexible and transparent substrate-anode combination is disclosed in United States Patent No. 5,844,363, which is incorporated by reference in its entirety. Anode 115 may be opaque and / or reflective. A reflective anode 115 may be preferred for some top-emitting devices, to increase the amount of light emitted from the top of the device. The material and thickness of anode 115 may be chosen to obtain desired conductive and optical properties. Where anode 115 is transparent, there may be a range of thickness for a particular material that is thick enough to provide the desired conductivity, yet thin enough to provide the desired degree of transparency. Other anode materials and structures may be used.

[00028]   Hole transport layer 125 may include a material capable of transporting holes. Hole transport occurs predominantly through the highest occupied molecular orbital (HOMO) levels of the "charge carrying component" of the hole transporting layer. This component may be the base material of the hole transport layer 125, or it may be a dopant. Hole transport layer 125 may be intrinsic (undoped), or doped. Doping may be used to enhance conductivity.. α-NPD and TPD are examples of intrinsic hole transport layers. An example of a p-doped hole transport layer is m-MTDATA doped with F4-TCNQ at a molar ratio of 50:1, as disclosed in United States Patent Application No. 10/173,682 to Forrest et al., which is incorporated by reference in its entirety. Other hole transport layer materials and structures may be used.

[00029]   As disclosed herein, emissive layer 135 includes an organic material capable of emitting photons of light when electrons drop from a lowest unoccupied molecular orbital (LUMO) of layer 135 where they combine with holes in the highest occupied molecular

5   orbital of layer 135. Accordingly, a current flow passed between anode 115 and cathode 160 through emissive layer 135 can produce an emission of light. In a present embodiment, emissive layer 135 comprises a phosphorescent emissive material such as those disclosed herein. Phosphorescent materials are preferred over fluorescenct materials because of the higher luminescent efficiencies associated with such materials.

10

[00030]   Emissive layer 135 may comprise a host material capable of transporting electrons and / or holes, doped with an emissive material that may trap electrons, holes, and / or excitons, such that excitons relax from the emissive material via a photoemissive mechanism. Emissive layer 135 may comprise a single material that combines transport and

15   emissive properties. Whether the emissive material is a dopant or a major constituent, emissive layer 135 may comprise other materials, such as dopants that tune the emission of the emissive material. Emissive layer 135 may include a plurality of emissive materials capable of, in combination, emitting a desired spectrum of light. Examples of phosphorescent emissive materials include $Ir(ppy)_3$. Examples of fluorescent emissive

20   materials include DCM and DMQA. Examples of host materials include Alq_3, CBP and mCP. Examples of emissive and host materials are disclosed in U.S. Patent No. 6,303,238 to Thompson et al., which is incorporated by reference in its entirety. Emissive material may be included in emissive layer 135 in a number of ways. For example, an emissive small molecule may be incorporated into a polymer. Other emissive layer materials and structures

25   may be used.

[00031]   Electron transport layer 140 may comprise a material capable of transporting electrons. Electron transport layer 140 may be intrinsic (undoped), or doped. Doping may be used to enhance conductivity. Alq_3 is an example of an intrinsic electron transport layer. An

30   example of an n-doped electron transport layer material is BPhen doped with Li at a molar ratio of 1:1, as disclosed in United States Patent Application No. 10/173,682 to Forrest et al., which is incorporated by reference in its entirety. Other electron transport layers materials

and structures may be used. The charge carrying component of the electron transport layer may be selected such that electrons can be efficiently injected from the cathode into the LUMO (Lowest Unoccupied Molecular Orbital) energy level of the electron transport layer. Electron transport occurs predominantly through the lowest unoccupied molecular orbit

5   (LUMO) levels of the "charge carrying component" of the electron transport layer. The "charge carrying component" is the material responsible for the LUMO that actually transports electrons. This component may be the base material, or it may be a dopant. The LUMO level of an organic material may be generally characterized by the electron affinity of that material while the relative electron injection efficiency of a cathode may be generally

10   characterized in terms of the work function of the cathode material. Accordingly, the preferred properties of an electron transport layer and the adjacent cathode may be specified in terms of the electron affinity of the charge carrying component of the ETL and the work function of the cathode material. In particular, so as to achieve high electron injection efficiency, the work function of the cathode material is preferably not greater than the

15   electron affinity of the charge carrying component of the electron transport layer by more than about 0.75 eV, more preferably, by not more than about 0.5 eV. Similar considerations apply to any layer into which electrons are being injected.

[00032]   Cathode 160 may be any suitable material or combination of materials known

20   to the art, such that cathode 160 is capable of conducting electrons and injecting them into the organic layers of device 100. Cathode 160 may be transparent or opaque, and may be reflective. Metals and metal oxides are examples of suitable cathode materials. Cathode 160 may be a single layer, or may have a compound structure. Figure 1 shows a compound cathode 160 having a thin metal layer 162 and a thicker conductive metal oxide layer 164. In

25   a compound cathode, preferred materials for the thicker layer 164 include ITO, IZO, and other materials known to the art. U.S. Patent Nos. 5,703,436 and 5,707,745, which are incorporated by reference in their entireties, disclose examples of cathodes including compound cathodes having a thin layer of metal such as Mg:Ag with an overlying transparent, electrically-conductive, sputter-deposited ITO layer. The part of cathode 160

30   that is in contact with the underlying organic layer, whether it is a single layer cathode 160, the thin metal layer 162 of a compound cathode, or some other part, is preferably made of a material having a work function lower than about 4 eV (a "low work function material").

Other cathode materials and structures may be used.

[00033]   Blocking layers may be used to reduce the number of charge carriers (electrons or holes) and / or excitons that leave the emissive layer. An electron blocking layer 130 may be disposed between emissive layer 135 and the hole transport layer 125, to block electrons from leaving emissive layer 135 in the direction of hole transport layer 125. Similarly, a hole blocking layer 140 may be disposed between emissive layer 135 and electron transport layer 145, to block holes from leaving emissive layer 135 in the direction of electron transport layer 140. Blocking layers may also be used to block excitons from diffusing out of the emissive layer.

[00034]   The theory and use of blocking layers is described in more detail in United States Patent No. 6,097,147 and United States Patent Application No. 10/173,682 to Forrest et al., which are incorporated by reference in their entireties. The conventional "blocking layer" is generally believed to reduce the number of charge carriers and / or excitons that leave the emissive layer by presenting an energy barrier that the charge carrier or exciton has difficulty surmounting. For example, hole transport is generally thought to be related to the Highest Occupied Molecular Orbital (HOMO) of an organic semiconductor. A "hole blocking" material may therefore be generally considered as a material that has a HOMO energy level significantly less than that of the material from which the holes are being blocked. A first HOMO energy level is considered "less than" a second HOMO energy level if it is lower on a conventional energy level diagram, which means that the first HOMO energy level would have a value that is more negative than the second HOMO energy level. For example, according to the density functional theory (DFT) calculation (B3LYP 6-31G*) using the Spartan 02 software package, Ir(ppy)$_3$ has a HOMO energy level of -4.85 eV. BCP has a HOMO energy level of −5.87 eV, which is 1.02 eV less than that of Ir(ppy)$_3$, making it an excellent hole blocker. ZrQ$_4$ has a HOMO energy level of -5.00, only 0.15 eV less than that of Ir(ppy)$_3$, such that little or no hole blocking is expected. mer-GaQ$_3$ has a HOMO energy level of -4.63 eV, which is greater than that of Ir(ppy)$_3$, such that no hole blocking at all is expected.

[00035]   If the emissive layer includes different materials with different energy levels,

the effectiveness of these various materials as hole blocking layers may be different, because it is the difference in HOMO energy levels between the blocking layer and the blocked layer that is significant, not the absolute HOMO energy level. The absolute HOMO level, however, may be useful in determining whether a compound will be a good hole blocker for

5   particular emissive layers. For example, a material having a HOMO energy level of about - 5.15 eV or less may be considered a reasonable hole blocking material for Ir(ppy)3, which is a representative emissive material. Generally, a layer having a HOMO energy level that is at least 0.25 eV less than that of an adjacent layer may be considered as having some hole blocking properties. An energy level difference of at least 0.3 eV is preferred, and an energy

10   level difference of at least 0.7 eV is more preferred. Similarly, the energy of an exciton is generally believed to be related to the band gap of a material. An "exciton blocking" material may generally be thought of as a material having a band gap significantly larger than the material from which excitons are being blocked. For example, a material having a band gap that is about 0.1 eV or more larger than that of an adjacent material may be considered a good

15   exciton blocking material.

[00036]   Generally, injection layers are comprised of a material that may improve the injection of charge carriers from one layer, such as an electrode or an organic layer, into an adjacent organic layer. Injection layers may also perform a charge transport function. In

20   device 100, hole injection layer 120 may be any layer that improves the injection of holes from anode 115 into hole transport layer 125. CuPc is an example of a material that may be used as a hole injection layer from an ITO anode 115, and other anodes. In device 100, electron injection layer 150 may be any layer that improves the injection of electrons into electron transport layer 145. LiF / Al is an example of a material that may be used as an

25   electron injection layer into an electron transport layer from an adjacent layer. Other materials or combinations of materials may be used for injection layers. Depending upon the configuration of a particular device, injection layers may be disposed at locations different than those shown in device 100. More examples of injection layers are provided in U.S. Patent Application Serial No. 09/931,948 to Lu et al., which is incorporated by reference in

30   its entirety. A hole injection layer may comprise a solution deposited material, such as a spin-coated polymer, e.g., PEDOT:PSS, or it may be a vapor deposited small molecule material, e.g., CuPc or MTDATA.

[00037]   A hole injection layer (HIL) may planarize or wet the anode surface so as to provide efficient hole injection from the anode into the hole injecting material. A hole injection layer may also have a charge carrying component having HOMO (Highest

5   Occupied Molecular Orbital) energy levels that favorably match up, as defined by their herein-described relative ionization potential (IP) energies, with the adjacent anode layer on one side of the HIL and the hole transporting layer on the opposite side of the HIL. Using a doped HIL allows the dopant to be selected for its electrical properties, and the host to be selected for morphological properties such as wetting, flexibility, toughness, etc. Preferred

10   properties for the HIL material are such that holes can be efficiently injected from the anode into the HIL material. In particular, the charge carrying component of the HIL preferably has an IP not more than about 0.7 eV greater that the IP of the anode material. More preferably, the charge carrying component has an IP not more than about 0.5 eV greater than the anode material. Similar considerations apply to any layer into which holes are being injected. HIL

15   materials are distinguished from conventional hole transporting materials that are typically used in the hole transporting layer of an OLED in that such HIL materials may have a hole conductivity that is substantially less than the hole conductivity of conventional hole transporting materials. The thickness of the HIL of the present invention may be thick enough to help planarize or wet the surface of the anode layer. For example, an HIL

20   thickness of as little as 10 nm may be acceptable for a very smooth anode surface. However, since anode surfaces tend to be very rough, a thickness for the HIL of up to 50 nm may be desired in some cases.

[00038]   A protective layer may be used to protect underlying layers during subsequent

25   fabrication processes. For example, the processes used to fabricate metal or metal oxide top electrodes may damage organic layers, and a protective layer may be used to reduce or eliminate such damage. In device 100, protective layer 155 may reduce damage to underlying organic layers during the fabrication of cathode 160. Preferably, a protective layer has a high carrier mobility for the type of carrier that it transports (electrons in device

30   100), such that it does not significantly increase the operating voltage of device 100. CuPc, BCP, and various metal phthalocyanines are examples of materials that may be used in protective layers. Other materials or combinations of materials may be used. The thickness

of protective layer 155 is preferably thick enough that there is little or no damage to underlying layers due to fabrication processes that occur after organic protective layer 160 is deposited, yet not so thick as to significantly increase the operating voltage of device 100. Protective layer 155 may be doped to increase its conductivity. For example, a CuPc or BCP protective layer 160 may be doped with Li. A more detailed description of protective layers may be found in U.S. Patent Application Serial No. 09/931,948 to Lu et al., which is incorporated by reference in its entirety.

[00039]   Figure 2 shows an inverted OLED 200. The device includes a substrate 210, an cathode 215, an emissive layer 220, a hole transport layer 225, and an anode 230. Device 200 may be fabricated by depositing the layers described, in order. Because the most common OLED configuration has a cathode disposed over the anode, and device 200 has cathode 215 disposed under anode 230, device 200 may be referred to as an "inverted" OLED. Materials similar to those described with respect to device 100 may be used in the corresponding layers of device 200. Figure 2 provides one example of how some layers may be omitted from the structure of device 100.

[00040]   The simple layered structure illustrated in Figures 1 and 2 is provided by way of non-limiting example, and it is understood that embodiments of the invention may be used in connection with a wide variety of other structures. The specific materials and structures described are exemplary in nature, and other materials and structures may be used. Functional OLEDs may be achieved by combining the various layers described in different ways, or layers may be omitted entirely, based on design, performance, and cost factors. Other layers not specifically described may also be included. Materials other than those specifically described may be used. Although many of the examples provided herein describe various layers as comprising a single material, it is understood that combinations of materials, such as a mixture of host and dopant, or more generally a mixture, may be used. Also, the layers may have various sublayers. The names given to the various layers herein are not intended to be strictly limiting. For example, in device 200, hole transport layer 225 transports holes and injects holes into emissive layer 220, and may be described as a hole transport layer or a hole injection layer. In one embodiment, an OLED may be described as having an "organic layer" disposed between a cathode and an anode. This organic layer may

comprise a single layer, or may further comprise multiple layers of different organic materials as described, for example, with respect to Figures 1 and 2.

[00041]   Structures and materials not specifically described may also be used, such as

5   OLEDs comprised of polymeric materials (PLEDs) such as disclosed in U.S. Pat. No. 5,247,190, Friend et al., which is incorporated by reference in its entirety. By way of further example, OLEDs having a single organic layer may be used. OLEDs may be stacked, for example as described in U.S. Patent No. 5,707,745 to Forrest et al, which is incorporated by reference in its entirety. The OLED structure may deviate from the simple layered structure

10   illustrated in Figures 1 and 2. For example, the substrate may include an angled reflective surface to improve out-coupling, such as a mesa structure as described in U.S. Patent No. 6,091,195 to Forrest et al., and / or a pit structure as described in U.S. Patent No. 5,834,893 to Bulovic et al., which are incorporated by reference in their entireties.

15   [00042]   Unless otherwise specified, any of the layers of the various embodiments may be deposited by any suitable method. For the organic layers, preferred methods include thermal evaporation, ink-jet, such as described in U.S. Patent Nos. 6,013,982 and 6,087,196, which are incorporated by reference in their entireties, organic vapor phase deposition (OVPD), such as described in U.S. Patent No. 6,337,102 to Forrest et al., which is

20   incorporated by reference in its entirety, and deposition by organic vapor jet printing (OVJP), such as described in U.S. Patent Application No. 10/233,470, which is incorporated by reference in its entirety. Other suitable deposition methods include spin coating and other solution based processes. Solution based processes are preferably carried out in nitrogen or an inert atmosphere. For the other layers, preferred methods include thermal evaporation.

25

[00043]   Preferred patterning methods include deposition through a mask, cold welding such as described in U.S. Patent Nos. 6,294,398 and 6,468,819, which are incorporated by reference in their entireties, and patterning associated with some of the deposition methods such as ink-jet and OVJD. Other methods may also be used. The materials to be deposited

30   may be modified to make them compatible with a particular deposition method. For example, substituents such as alkyl and aryl groups, branched or unbranched, and preferably containing at least 3 carbons, may be used in small molecules to enhance their ability to

undergo solution processing. Substituents having 20 carbons or more may be used, and 3-20 carbons is a preferred range. Materials with asymmetric structures may have better solution processibility than those having symmetric structures, because asymmetric materials may have a lower tendency to recrystallize. Dendrimer substituents may be used to enhance the

5   ability of small molecules to undergo solution processing.

[00044]   Devices fabricated in accordance with embodiments of the invention may be incorporated into a wide variety of consumer products, including flat panel displays, computer monitors, televisions, billboards, lights for interior or exterior illumination and / or

10   signaling, heads up displays, fully transparent displays, flexible displays, laser printers, telephones, cell phones, personal digital assistants (PDAs), laptop computers, digital cameras, camcorders, viewfinders, micro-displays, vehicles, a large area wall, theater or stadium screen, or a sign. Various control mechanisms may be used to control devices fabricated in accordance with the present invention, including passive matrix and active matrix. Many of

15   the devices are intended for use in a temperature range comfortable to humans, such as 18 degrees C to 30 degrees C, and more preferably at room temperature (20 - 25 degrees C).

[00045]   The materials and structures described herein may have applications in devices other than OLEDs. For example, other optoelectronic devices such as organic solar cells and

20   organic photodetectors may employ the materials and structures. More generally, organic devices, such as organic transistors, may employ the materials and structures.

[00046]   As used herein, "solution processible" means capable of being dissolved, dispersed, or transported in and/or deposited from a liquid medium, either in solution or

25   suspension form.

[00047]   One application for phosphorescent emissive molecules is a full color display. Industry standards for such a display call for pixels adapted to emit particular colors, referred to as "saturated" colors. In particular, these standards call for saturated red, green, and blue

30   pixels. Color may be measured using CIE coordinates, which are well known to the art. CIE coordinates are described in H. Zollinger, "Color Chemistry" VCH Publishers, 1991 and H, J, A, Dartnall, J. K. Bowmaker, and J. D. Mollon, Proc. Roy. Soc. B (London), 1983, 220, 115-

130, which are incorporated by reference. For example, the NTSC standard calls for a saturated blue having CIE (0.155, 0.07). The SRGB standard calls for CIE (0.15, 0.06). Other industry standards may call for slightly different CIE coordinates.

5   [00048]   The present invention will now be described in detail for specific preferred embodiments of the invention. These embodiments are intended to be illustrative and the invention is not limited in scope to the specific preferred embodiments described.

[00049]   The devices of the present invention comprise at least one phosphorescent

10   organometallic emissive material. The emissive material comprises one or more ligands that produce a hypsochromic (blue) shift in the emission spectrum of light emitted by an associated emitting ligand. Organometallic compound of the present invention can be represented by the following general structure Formula I:
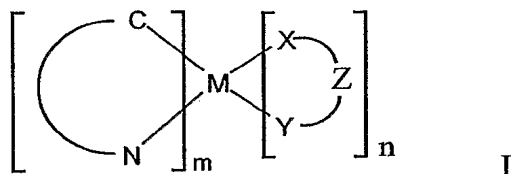
15

in which C-N is a cyclometallated ligand, M is a metal with an atomic weight of greater than 40, X and Y are independently selected groups incorporating a heteroatom, Z is a divalent linker, and m and n are integers selected from 1 and 2. The sum of n + m is 2 or 3. X-Z-Y is an anionic ligand. Preferably, M has an atomic weight of greater than 72.

20

[00050]   The compounds of the present invention comprises a transition metal which produces phosphorescent emission from a mixture of MLCT and $\pi - \pi^*$ ligand states. Suitable transition metals include but are not limited to Ir, Pt, Pd, Rh, Re, Os, Tl, Pb, Bi, In, Sn, Sb, Te, Au, and Ag and other heavy metals with an atomic number of at least 40.

25

[00051]   The divalent linker, Z, can be represented by the general structure $JR'_pR''_q$ wherein J is hydrogen or a metal or non-metal, selected as appropriate to bond to X and Y, R' and R" are independently H, alkyl, aryl, heteroaryl, halogen, hydroxy, alkoxy, aryloxy, amino, alkylamino, arylamino, sulfido, alkylsulfido, arylsulfido, phophino, alkylphosphino or

arylphosphino and p and q are integers between 0 and 2. Without limiting the scope of the invention, Z can therefore be H, Ag, Au, BR'R", AlR'R" or ZnR' where R' and R" can be selected from the group consisting of alkyl, aryl and heteroaryl, and R' and R" can be interlinked to form a bidentate ligand. Preferably R' and R" are C_1 - C_6 alkyl, aryl, heteroaryl,

5   hydroxy, alkoxy, aryloxy, amino, alkylamino, arylamino, sulfido, alkylsulfido, arylsulfido, phosphino, alkylphosphino or arylphosphino. More preferably R' and R" are C_1 - C_3 alkyl, aryl, heteroaryl, alkoxy, aryloxy, alkylamino, arylamino, alkylsulfido, arylsulfido, alkylphosphino or arylphosphino.

10

[00052]   In one embodiment, the formal negative charge is located on the J in $JR'_pR"_q$. Such a chemical structure implies that the X-Ir and the Y-Ir bond are both dative bonds in nature. As a result, there is a formal positive charge on the Ir atom:
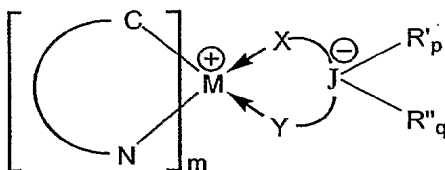
15   In such a Zwitterionic structure, it is believed that a blue shift of the metal complex phosphorescence can result. For example, as shown in Table 1, the emission peak of entry 3 is "blue shifted" by 30 nm relative to the comparative example which has a traditional acetylacetonate (acac) ancillary ligand.

20   [00053]   In a preferred embodiment of the present invention, X and Y are heterocycles selected to have functionality appropriate for coordinating to M. In a further preferred embodiment X and Y are selected from the group consisting of pyrazoles, triazoles, tetrazoles, thiazoles, furans and pyridines. X and Y can be the same or different.

25   [00054]   In a further embodiment of the present invention X and Y are selected from the group consisting of OR, SR, NR_2 and PR_2, wherein R is selected from the group consisting of H, alkyl, aryl, heteroaryl, halogen, alkoxy, amino, alkylamino, arylamino, sulfido, alkylsulfido, arylsulfido, phophino, alkylphosphino or arylphosphino

18

[00055]   In preferred embodiments of the present invention J is zinc, silver, gold, aluminum, boron or hydrogen. In more preferred embodiments J is boron or hydrogen.

[00056]   The compounds of the present invention are, in a preferred embodiment, intended for use in a luminescent device. Generally such a device will comprise an organic layer which comprises the compound of the present invention disposed in some manner between two electrodes, one a cathode and the other an anode.

[00057]   In a preferred embodiment the emissive layer comprises host material. The host material may comprise an electron transporting material that conducts charge primarily by the transport of electrons. Alternatively the host material may comprise a hole transporting material that conducts charge primarily by the transport of holes. The organometallic compound described can be doped in the host material of the light emitting device. The organometallic compound has a lowest triplet excited state with a radiative decay of greater than approximately 1×10^5 per second and the energy level of the lowest triplet excited state of the host material is higher than the energy level of the lowest triplet state of the organometallic compound. In a preferred embodiment of the present invention the energy difference between the lowest triplet excited state of the organometallic compound of the present invention and a corresponding relaxed state of the organometallic compound corresponds with a wavelength of less than approximately 520 nm. More preferably the energy difference between the lowest triplet excited state of the organometallic compound of the present invention and a corresponding relaxed state of the organometallic compound corresponds with a wavelength of between approximately 420 nm and approximately 480 nm.

[00058]   The organic light emitting devices of the present invention may be fabricated using methods and materials known in the art. Representative OLED methods, materials and configurations are described in U.S. Patent Nos. 5,703,436; 5,707,745, 5,834,893; 5,844,363; 6,097,147; and 6,303,238; each of which is incorporated by reference in its entirety.

[00059]   The compounds described have been represented throughout by their monomeric structure. As is well known to those in the art, the compounds may also be present as dimers, trimers or dendrimers.

5   [00060]   In one embodiment of the invention, the phosphorescent organometallic emissive material may be represented by the general formula II :

(II)
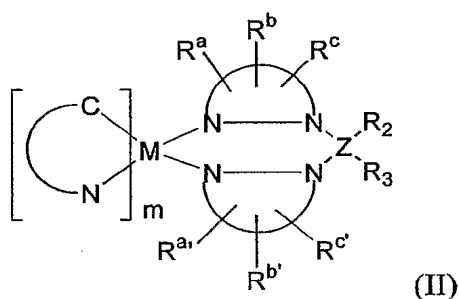
10   wherein

 , also abbreviated C-N, is a cyclometallated ligand,

M is a metal with an atomic weight of greater than 40,

Z is a divalent linker,

R_2 and R_3 are independently H, alkyl, aryl, heteroaryl, halogen, hydroxy, alkoxy, aryloxy,

15   amino, alkylamino, arylamino, sulfido, alkylsulfido, arylsulfido, phophino, alkylphosphino or arylphosphino

R_a, R_b, R_c, R'_a, R'_b and R'_c, if present, are selected independently from H, alkyl, aryl, heteroaryl, halogen, alkoxy, amino, alkylamino, arylamino, sulfido, alkylsulfido, arylsulfido, phophino, alkylphosphino or arylphosphino,
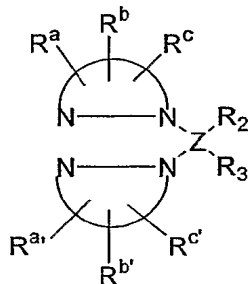
20   with the proviso that   is anionic.

The ring structure represented by is a five- or six-membered ring comprising two adjacent nitrogens. The ring may also contain an additional hetero atom. Any two adjacent substituted positions on the ring may together form, independently, a fused 5- to 6-member cyclic group, wherein said cyclic group is cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl. Z is a metal or non-metal, and preferably is Ag, Zn, Al, B, Ga, In, Cd, Hg, Cu, or Au.

[00061]   In a further embodiment of the invention, X and Y are both a pyrazole or substituted pyrazole resulting in an emissive material having the Formula III:
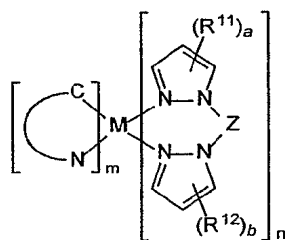
III

wherein C-N is a cyclometallated ligand, and M, Z, m and n are as described above for the Formula I. Each R^{11} and R^{12} is independently selected from alkyl, alkenyl, alkynyl, alkylaryl, CN, CF_3, CO_2R, C(O)R, NR_2, NO_2, OR, halo, aryl, heteroaryl, substituted aryl, substituted heteroaryl or a heterocyclic group, and additionally, or alternatively, any two adjacent substituted positions together form, independently, a fused 5- to 6-member cyclic group, wherein said cyclic group is cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl, and wherein the fused 5- to 6-member cyclic group cyclic group may be optionally substituted with one or more of alkyl, alkenyl, alkynyl, alkylaryl, CN, CF_3, CO_2R, C(O)R, NR_2, NO_2 , OR, or halo; each R is independently alkyl, alkenyl, alkynyl, aralkyl, and aryl; and subscript a and b are independently selected from 0, 1, 2, and 3.

[00062]   In a further embodiment of the invention, X and Y are both a pyrazole and Z is H resulting in an emissive material of the formula IV:

IV

wherein C-N is a cyclometallated ligand, and M, m and n are as described above for the Formula I. Each R^{11} and R^{12} is independently selected from alkyl, alkenyl, alkynyl, alkylaryl, CN, CF_3, CO_2R, $C(O)R$, NR_2, NO_2, OR, halo, aryl, heteroaryl, substituted aryl, substituted

5 heteroaryl or a heterocyclic group, and additionally, or alternatively, any two adjacent substituted positions together form, independently, a fused 5- to 6-member cyclic group, wherein said cyclic group is cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl, and wherein the fused 5- to 6-member cyclic group cyclic group may be optionally substituted with one or more of alkyl, alkenyl, alkynyl, alkylaryl, CN, CF_3, CO_2R, $C(O)R$, NR_2, NO_2 , OR, or halo;

10 each R is independently alkyl, alkenyl, alkynyl, aralkyl, and aryl; and

subscript a and b are independently selected from 0, 1, 2, and 3.

[00063]   In a preferred embodiment, the pyrazole rings of Formula IV are unsubstituted giving a compound of the formula IV_a:

15
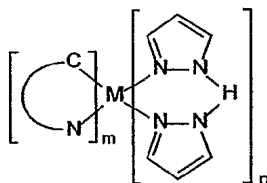
IV_a

wherein C-N is a cyclometallated ligand, and M, m and n are as described above for the Formula I. In a further preferred embodiment, M is Ir and m =2 and n=1.

20 [00064]   A further embodiment of the invention is represented by the compound of Formula V:
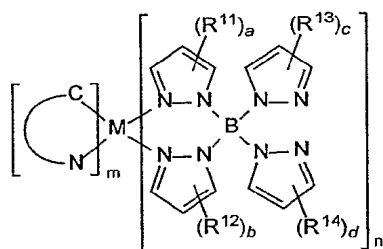
V

wherein C-N is a cyclometallated ligand, and M, m and n are as described above for the Formula I. Each R^{11}, R^{12}, R^{13}, and R^{14} is independently selected from alkyl, alkenyl, alkynyl, alkylaryl, CN, CF_3, CO_2R, C(O)R, NR_2, NO_2, OR, halo, aryl, heteroaryl, substituted aryl,

5   substituted heteroaryl or a heterocyclic group, and additionally, or alternatively, any two adjacent substituted positions together form, independently, a fused 5- to 6-member cyclic group, wherein said cyclic group is cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl, and wherein the fused 5- to 6-member cyclic group cyclic group may be optionally substituted with one or more of alkyl, alkenyl, alkynyl, alkylaryl, CN, CF_3, CO_2R, C(O)R, NR_2, NO_2 ,

10   OR, or halo;

each R is independently alkyl, aryl and heteroarl; and

subscript a, b, c, and d are independently selected from 0, 1, 2, and 3.

[00065]   In a preferred embodiment, the pyrazole rings of Formula V are unsubstituted,

15   M is Ir, m is 2 and n is 1, giving a compound of the formula V_a:

V_a

wherein C-N is a cyclometallated ligand.

20
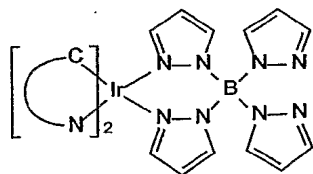
[00066]   .In another embodiment of the invention the emissive material may be represented by the formula (VI)
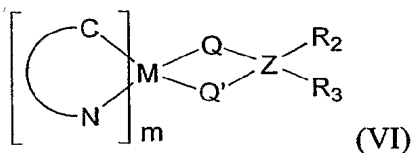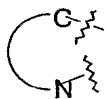
23

(VI)

wherein

 is a cyclometallated ligand,

M is a metal with an atomic weight of greater than 40,

Z is a divalent linker,

m is 1 or 2,

Q and Q' are heteroatoms, and,

R_2 and R_3 are hydrogen, halogens, heteroatoms or heterocycles.

[00067]   The cyclometallated ligand, C-N, may be selected from those known in the art. Preferred cyclometallating ligands are 2-phenylpyridines and phenylpyrazoles
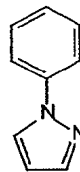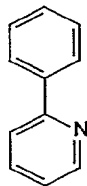
and derivatives thereof. The phenylpyridine or phenylpyrazole cyclometallated ligand my be optionally substituted with one or more alkyl, alkenyl, alkynyl, alkylaryl, CN, CF_3, CO_2R, C(O)R, NR_2, NO_2, OR, halo, aryl, heteroaryl, substituted aryl, substituted heteroaryl or a heterocyclic group, and additionally, or alternatively, any two adjacent substituted positions together form, independently, a fused 5- to 6-member cyclic group, wherein said cyclic group is cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl, and wherein the fused 5- to 6-member cyclic group cyclic group may be optionally substituted with one or more of alkyl, alkenyl, alkynyl, alkylaryl, CN, CF_3, CO_2R, C(O)R, NR_2, NO_2 , OR, or halo; and each R is independently alkyl, alkenyl, alkynyl, aralkyl, and aryl;

[00068]   In the present disclosure the following terms are used.

[00069]   The term "halo" or "halogen" as used herein includes fluorine, chlorine, bromine and iodine.

[00070]   The term "alkyl" as used herein contemplates both straight and branched chain alkyl radicals. Preferred alkyl groups are those containing from one to fifteen carbon atoms and includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, and the like. Additionally, the alkyl group may be optionally substituted with one or more substituents selected from halo, CN, CO_2R, C(O)R, NR_2, cyclic-amino, NO_2, and OR.

[00071]   The term "cycloalkyl" as used herein contemplates cyclic alkyl radicals. Preferred cycloalkyl groups are those containing 3 to 7 carbon atoms and includes cyclopropyl, cyclopentyl, cyclohexyl, and the like. Additionally, the cycloalkyl group may be optionally substituted with one or more substituents selected from halo, CN, CO_2R, C(O)R, NR_2, cyclic-amino, NO_2, and OR.

[00072]   The term "alkenyl" as used herein contemplates both straight and branched chain alkene radicals. Preferred alkenyl groups are those containing two to fifteen carbon atoms. Additionally, the alkenyl group may be optionally substituted with one or more substituents selected from halo, CN, CO_2R, C(O)R, NR_2, cyclic-amino, NO_2, and OR.

[00073]   The term "alkynyl" as used herein contemplates both straight and branched chain alkyne radicals. Preferred alkyl groups are those containing two to fifteen carbon atoms. Additionally, the alkynyl group may be optionally substituted with one or more substituents selected from halo, CN, CO_2R, C(O)R, NR_2, cyclic-amino, NO_2, and OR.

[00074]   The term "alkylaryl" as used herein contemplates an alkyl group which has as a substituent an aromatic group. Additionally, the alkylaryl group may be optionally substituted on the aryl with one or more substituents selected from halo, CN, CO_2R, C(O)R, NR_2, cyclic-amino, NO_2, and OR.

[00075]   **Cyclometallated ligand** is a term well known in the art and includes but is not limited to MeOfppy, fppy, and NMe$_2$fppy.

[00076]   **Heterocyclic** refers to a 3 to 7 membered ring containing at least one heteroatom. This includes aromatic rings including but not limited to pyrazole, triazole, tetrazole, thiazole, furan, thiophene, pyridine, and non-aromatic rings including but not limited to piperazine, piperidine, and pyrrolidine. The groups of the present invention can be substituted or unsubstituted. Preferred substituents include but are not limited to alkyl, alkoxy, aryl.

[00077]   **Heteroatom** refers to S, O, N, P.

[00078]   Preferred alkyl groups are C_1 through C_6 alkyls. Similarly C_1 through C_6 alkoxy and aryl groups are preferred. C_1 through C_6 heteroaryl, alkylamino, arylamino, alkylsulfido, arylsulfido, alkylphosphino or arylphosphino groups are preferable. More preferable are C_1 through C_3 alkyls. Similarly C_1 through C_6 alkoxy and aryl groups are preferred. C_1 through C_6 heteroaryl, alkylamino, arylamino, alkylsulfido, arylsulfido, alkylphosphino or arylphosphino.

[00079]   **Divalent linker** refers to an atom or group to which two atoms or groups can be bonded such that overall the group X-Z-Y is one anionic ligand.

[00080]   **Pyrazole** includes substituted or unsubstituted pyrazole.

[00081]   **Triazole** includes substituted or unsubstituted triazole.

[00082]   **Tetrazole** includes substituted or unsubstituted tetrazole.

[00083]   **Thiazole** includes substituted or unsubstituted thiazole.

[00084]   **Pyridine** includes substituted or unsubstituted pyridine.

[00085]   **Aryl** alone or in combination includes carbocyclic aromatic systems or heterocyclic aromatic systems (also known as heteroaryl). The systems may contain one, two or three rings wherein each ring may be attached together in a pendent manner or may be fused. Preferably the rings have 5 or 6 members.

[00086]   Alkoxy includes linear or branched alkoxy groups, preferably C_1 to C_6 alkoxy groups, more preferably C_1 to C_3 alkoxy groups.

[00087]   **Substituted** refers to any level of substitution although mono-, di- and tri-substitutions are preferred. Preferred substituents include hydrogen, halogen, aryl, alkyl and heteroaryl.

[00088]   **pz** is pyrazole.

[00089]   **MeOfppy** is methoxy(difluorophenyl)pyridine.

[00090]   **fppy** is (difluorophenyl)pyridine.

[00091]   **dmafppy** is dimethylamino(difluorophenyl)pyridine.

Material Definitions:

[00092]   As used herein, abbreviations refer to materials as follows:

CBP:	4,4'-N,N-dicarbazole-biphenyl
m-MTDATA	4,4',4"-tris(3-methylphenylphenlyamino)triphenylamine
Alq$_3$:	8-tris-hydroxyquinoline aluminum
Bphen:	4,7-diphenyl-1,10-phenanthroline
n-BPhen:	n-doped BPhen (doped with lithium)
F$_4$-TCNQ:	tetrafluoro-tetracyano-quinodimethane
p-MTDATA:	p-doped m-MTDATA (doped with F$_4$-TCNQ)
Ir(ppy)$_3$:	tris(2-phenylpyridine)-iridium
Ir(ppz)$_3$:	tris(1-phenylpyrazoloto,N,C(2')iridium(III)
BCP:	2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline
TAZ:	3-phenyl-4-(1'-naphthyl)-5-phenyl-1,2,4-triazole
CuPc:	copper phthalocyanine.
ITO:	indium tin oxide
NPD:	N,N'-diphenyl-N-N'-di(1-naphthyl)-benzidine
TPD:	N,N'-diphenyl-N-N'-di(3-toly)-benzidine
BAlq:	aluminum(III)bis(2-methyl-8-quinolinato)4-phenylphenolate
mCP:	1,3-N,N-dicarbazole-benzene
DCM:	4-(dicyanoethylene)-6-(4-dimethylaminostyryl-2-methyl)-4H-pyran

DMQA:	N,N'-dimethylquinacridone
PEDOT:PSS :	an aqueous dispersion of poly(3,4-ethylenedioxythiophene) with polystyrenesulfonate (PSS)
ppz	1-phenylpyrazole
ppy	2-phenylpyridine

5

[00093]   It is understood that the various embodiments described herein are by way of example only, and are not intended to limit the scope of the invention. For example, many of the materials and structures described herein may be substituted with other materials and

10   structures without deviating from the spirit of the invention. It is understood that various theories as to why the invention works are not intended to be limiting. For example, theories relating to charge transfer are not intended to be limiting.

[00094]   The compounds described have been represented throughout by their

15   monomeric structure. As is well known to those in the art, the compounds may also be present as dimers, trimers or dendrimers.

Examples:

Synthesis of compound 1: (*MeOfppy*)₂Ir(pz₂Bpz₂):

(*MeOfppy*)Ir(pz₂Bpz₂)

20
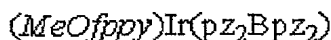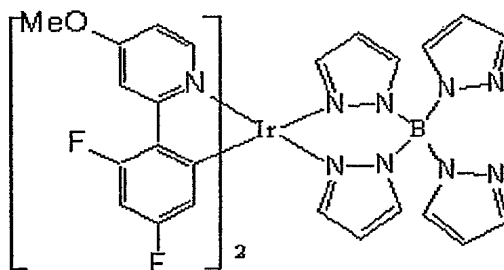
[00095]   [Ir(*MeOfppy*)₂Cl]₂ (1.0 g, 0.75 mmol) was dissolved in 50 mL of CH_2Cl_2 and a solution of 2.1 equiv. AgOTf (0.41 g, 1.6 mmol) in 50 ml of MeOH was added to yield a cream-colored slurry. After the slurry was stirred for 2 hours at room temperature, it was centrifuged to precipitate the AgCl and the decantate was evaporated to dryness to yield a

25   yellow, oily residue. The residue was dissolved in 50 ml CH_3CN, and 3 equiv. KBPz₄ (0.72

g, 2.26 mmol) was added to the solution. The solution was heated at 110 C for 18 hours under N$_2$, then filtered. The precipitate was washed with 50 mL CH$_2$Cl$_2$. The washed solution was collected and evaporated to dryness. Yield 0.8 g (*MeOfppy*)$_2$Ir(pz$_2$Bpz$_2$). The filtrate of CH$_3$CN solution was evaporated to dryness. After chromatography, a second crop of

5   (*MeOfppy*)$_2$Ir(pz$_2$Bpz$_2$) about 0.2 g was obtained.

[00096]   **Synthesis of compound 2: (*MeOfppy*)$_2$Ir(pz$_2$H):**
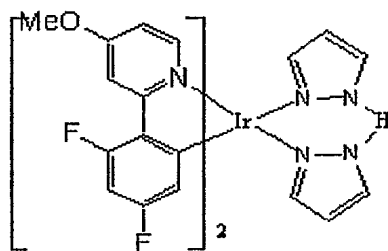
(*MeOfppy*)Ir(pz$_2$H)

[00097]   [Ir(*MeOfppy*)$_2$Cl]$_2$ (0.1 g, 0.075 mmol) was dissolved in 25 mL of CH$_2$Cl$_2$,

10   0.05 g pyrazole and 0.05 g excess MeONa were added to solution. After the solution was stirred for overnight at room temperature, it was filtered off. The filtrate was collected and evaporated to dryness. The crude product was recrystalized in CH$_2$Cl$_2$/MeOH to yield over 0.1 g clean (*MeOfppy*)$_2$Ir(pz$_2$H).

15   [00098]   **Synthesis of compound 3: (*fppy*)$_2$Ir(pz$_2$Bpz$_2$):**
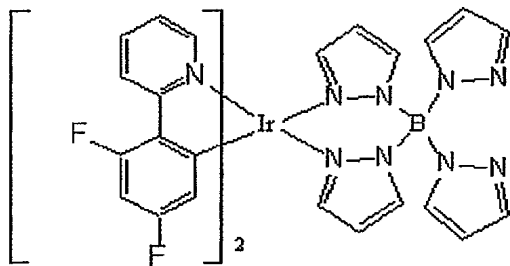
(*fppy*)Ir(pz$_2$Bpz$_2$)

[00099]   0.93 g [Ir(*fppy*)$_2$Cl]$_2$ was dissolved in 50 mL of CH$_2$Cl$_2$ and a solution of 0.5 g AgOTf in 50 ml of MeOH was added to yield a cream-colored slurry. After the slurry was stirred for 2 hours at room temperature, it was centrifuged to precipitate the AgCl and the

29

decantate was evaporated to dryness to yield a yellow, oily residue. The residue was
dissolved in 50 ml CH_3CN, and 0.85 $KBPz_4$ was added to the solution. The solution was
heated at 110 C for 18 hours under N_2, then filtered. The precipitate was washed with 50 mL
CH_2Cl_2. The washed solution was collected and evaporated to dryness. Yield 0.8 g

5   (*fppy*)$_2$Ir(pz$_2$Bpz$_2$).

[000100]   **Synthesis of compound 4: (*dmafppy*)$_2$Ir(pz$_2$BPz$_2$):**
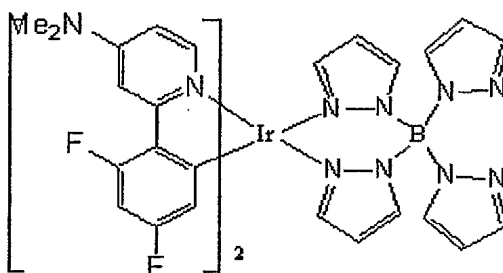
(*dmafppy*)Ir(pz$_2$Bpz$_2$)

[000101]   0.1 g [Ir(*dmafppy*)$_2$Cl]$_2$ was dissolved in 15 mL of CH_3CN and 0.04 g AgOTf
10   was added to yield a cream-colored slurry. After the slurry was stirred for 2 hours at room
temperature, it was centrifuged to precipitate the AgCl. 0.07 g $KBPz_4$ was added to the
decantante. The solution was heated at 110 C for 18 hours under N_2, then filtered. The
precipitate was washed with 20 mL CH_2Cl_2. The washed solution was collected and
evaporated to dryness. Yield 0.05 g (*dmafppy*)$_2$Ir(pz$_2$Bpz$_2$).

15

Device fabrication

[000102]   Devices 1 and 3, and the comparative example were fabricated by high
vacuum ($<10^{-7}$ Torr) thermal evaporation. Indium tin oxide (ITO) anode on glass was used as
the anode. The cathode consists of 10 Å of LiF followed by 1,000 Å of Al. All devices were
20   encapsulated with a glass lid sealed with an epoxy resin in a nitrogen glove box (<1 ppm of
H_2O and O_2) immediately after fabrication, and a moisture getter was incorporated inside the
package. The emission maxima and maximum luminous efficiency (in cd/A) are summarized
in following Table. For compound 2 and 4, the emission maxima are obtained from the
photoluminescence measured in CH_2Cl_2.

Device 1

[000103]   The organic stack consists of, from the anode to the cathode, 100 Å of copper

phthalocyanine (CuPc), 300 Å of 4,4'-bis[N-(1-naphthyl)-N-phenylamino]biphenyl (α-NPD),

5   300 Å of mCP doped with 6 wt% of Compound 1 as the emissive layer (EML), 400 Å of

aluminum(III)bis(2-methyl-8-quinolinato)4-phenylphenolate (BAlq).

Device 3

[000104]   The organic stack consists of, from the anode to the cathode, 100 Å of copper

10   phthalocyanine (CuPc), 300 Å of 4,4'-bis[N-(1-naphthyl)-N-phenylamino]biphenyl (α-NPD),

300 Å of mCP doped with 6 wt% of Compound 3 as the emissive layer (EML), 400 Å of

aluminum(III)bis(2-methyl-8-quinolinato)4-phenylphenolate (BAlq).

Comparative Example

15   [000105]   The organic stack consists of, from the anode to the cathode, 100 Å of copper

phthalocyanine (CuPc), 300 Å of 4,4'-bis[N-(1-naphthyl)-N-phenylamino]biphenyl (α-NPD),

300 Å of mCP doped with 6 wt% of the comparative example compound as the emissive

layer (EML), 400 Å of aluminum(III)bis(2-methyl-8-quinolinato)4-phenylphenolate (BAlq).

20   Table 1
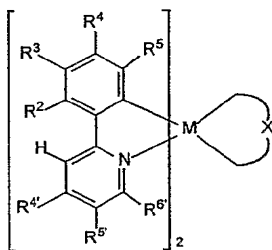
	M	R2	R3	R4	R5	R'4	R'5	R'6	(X) Ligand	Emission (nm)	OLED Max Efficiency (cd/A)
1	Ir	F	H	F	H	OMe	H	H	pz_2Bpz_2	450	3.5
2	Ir	F	H	F	H	OMe	H	H	pz_2H	462	
3	Ir	F	H	F	H	H	H	H	pz_2Bpz_2	455	7
4	Ir	F	H	F	H	NMe₂	H	H	pz_2Bpz_2	448	
Comparative Example	Ir	F	H	F	H	H	H	H	acac	485	5

Claims

1.   A compound represented by the Formula (I)
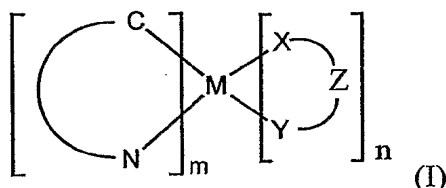
(I)

wherein

    is a cyclometallated ligand,

M is a metal with an atomic weight of greater than 40,

X and Y are each an independently selected from a heteroatom, heteroatom-containing group or heterocycle,

Z is a divalent linker,

Z is a group of the formula $JR'_pR''_q$

wherein J is hydrogen or a metal or a non-metal, R' and R" are independently, alkenyl, heteroaryl, hydroxy, alkoxy, aryloxy, amino, alkylamino, arylamino, sulfido, alkylsulfido, arylsulfido, phophino, alkylphosphino or arylphosphino and p and q are integers between 0 and 2.

m and n are integers selected from 1 and 2 wherein the sum of n + m is 2 or 3,
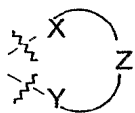
with the proviso that is anionic.

2.   The compound of claim 1, wherein J is boron.

3.   The compound of claim 1 wherein the heteroatom-containing group is selected from OR, SR, NR_2 and PR_2, wherein R is alkyl, aryl, or heteroaryl.

4.   The compound of claim 3, wherein R is a C_1-C_6 alkyl, aryl, or heteroaryl.

5.   The compound of claim 1, wherein R' and R" are heteroaryl.

6.   The compound of claim 5 wherein R' and R" are selected from the group consisting of alkyls, aryls, and pyrazoles and p and q are each 1.

7.   The compound of claim 4 wherein R' is pyrazole, R" is a pyrazole and p and q are each 1.

8.   The compound of claim 5 wherein X and Y are pyrazoles.

9.   The compound of claim 5, wherein Z is hydrogen.

10.   The compound of claim 1, wherein the heavy metal is selected from the group consisting of Ir, Pt, Pd, Rh, Re, Os, Tl, Pb, Bi, In, Sn, Sb, Te, Ag, and Au.

11.   The compound of claim 9 wherein the heavy metal is Ir.

12.   The compound of claim 9 wherein the heavy metal is Pt.

13.   The compound of claim 1, having the Formula III:
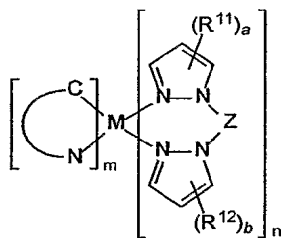
III

wherein each R^{11} and R^{12} is independently selected from alkyl, alkenyl, alkynyl, alkylaryl, CN, CF_3, CO_2R, $C(O)R$, NR_2, NO_2, OR, halo, aryl, heteroaryl, substituted aryl, substituted heteroaryl or a heterocyclic group, and additionally, or alternatively, any two adjacent substituted positions together form, independently, a fused 5- to 6-member cyclic group, wherein said cyclic group is cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl, and wherein the fused 5- to 6-member cyclic group cyclic group may be optionally substituted with one or more of alkyl, alkenyl, alkynyl, alkylaryl, CN, CF_3, CO_2R, $C(O)R$, NR_2, NO_2 , OR, or halo;
each R is independently alkyl, aryl, or heteroaryl; and
subscript a and b are independently selected from 0, 1, 2, and 3.

14.   The compound of claim 5, having the formula IV:
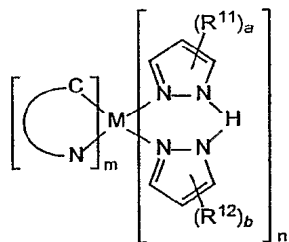
IV

15. The compound of claim 1, having the Formula V:
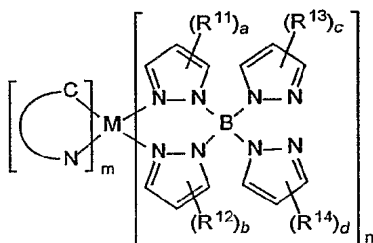
V

wherein each R^{11}, R^{12}, R^{13}, and R^{14} is independently selected alkyl, alkenyl, alkynyl, alkylaryl, CN, CF_3, CO_2R, $C(O)R$, NR_2, NO_2, OR, halo, aryl, heteroaryl, substituted aryl, substituted heteroaryl or a heterocyclic group, and additionally, or alternatively, any two adjacent substituted positions together form, independently, a fused 5- to 6-member cyclic group, wherein said cyclic group is cycloalkyl, cycloheteroalkyl, aryl, or heteroaryl, and wherein the fused 5- to 6-member cyclic group cyclic group may be optionally substituted with one or more of alkyl, alkenyl, alkynyl, alkylaryl, CN, CF_3, CO_2R, $C(O)R$, NR_2, NO_2, OR, or halo;

each R is independently alkyl, aryl and heteroarl; and

subscript *a*, *b*, *c*, and *d* are independently selected from 0, 1, 2, and 3.

16. A compound represented by the formula (I)

(I)

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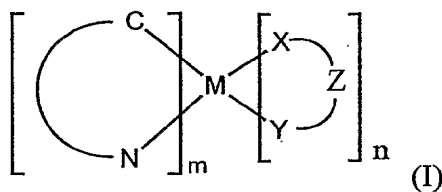
wherein

 is a cyclometallated ligand,

M is a metal with an atomic weight of greater than or equal to 40,

X and Y are each an independently selected heteroatom-containing group or heterocycle,

m and n are integers selected from 1 and 2 wherein the sum of n + m is 2 or 3,

Z is H or is denoted by $JR'_pR''_q$ wherein J is hydrogen or a metal or a non-metal, wherein J is selected from the group consisting of Al, Ga, In, Zn, Cd, Hg, Cu, Ag and Au. R' and R'' are independently H, alkyl, alkenyl, heteroaryl, halogen, hydroxy, alkoxy, aryloxy, amino, alkylamino, arylamino, sulfido, alkylsulfido, arylsulfido, phophino, alkylphosphino or arylphosphino and p and q are integers between 0 and 2,
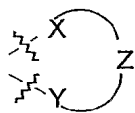
with the proviso that is anionic.

17. The compound of claim 16, wherein X and Y are heterocycles.

18. The compound of claim 17 wherein X and Y are pyrazoles.

19. The compound of claim 18 wherein R' is pyrazole, R'' is a pyrazole and p and q are each 1.

20. The compound of claim 16 wherein R' is selected from the group consisting of bidentate alkyl, aryl and carboxyl ligands and chelating coordination ligands, p is equal to 1 and q is equal to 0.

21. The compound of claim 16 wherein R' and R'' are selected from the group consisting of alkyls, aryls, and pyrazoles and p and q are each 1.

22. The compound of claim 16, wherein Z is hydrogen.

23. The compound of claim 16, wherein the heavy metal is selected from the group consisting of Ir, Pt, Pd, Rh, Re, Os, Tl, Pb, Bi, In, Sn, Sb, Te, Ag, and Au.

24. The compound of claim 23 wherein the heavy metal is Ir.

25. The compound of claim 23 wherein the heavy metal is Pt.

26. The compound of claim 16 having the formula (II).
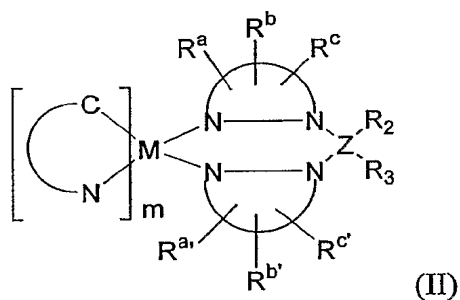
(II)

wherein

is a cyclometallated ligand,

M is a metal with an atomic weight of greater than 40,

Z is a divalent linker,

m is 1 or 2,

R_a, R_b, R_c, R'_a, R'_b and R'_c, if present, are selected from H, alkyl, aryl, heteroaryl, halogen, alkoxy, amino, alkylamino, arylamino, sulfido, alkylsulfido, arylsulfido, phophino, alkylphosphino or arylphosphino,
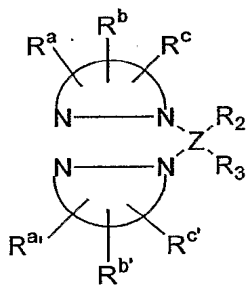
with the proviso that   is anionic.

27.   A light emitting device comprising an organic layer, the organic layer comprising a composition represented by the structure:
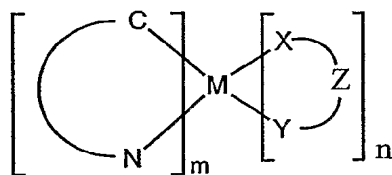
wherein
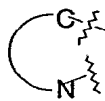
 is a cyclometallated ligand,

M is a metal with an atomic weight of greater than 40,

X and Y are each an independently selected heteroatom-containing group or heterocycle,

Z is a divalent linker,

m and n are integers selected from 1 and 2 wherein the sum of n + m is 2 or 3,
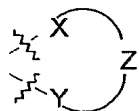
with the proviso that is anionic.

28.   The light emitting device of claim 27, wherein Z is represented by the general structure $JR'_pR''_q$ wherein J is hydrogen, a metal or a non-metal, R' and R'' are independently H, alkyl, alkenyl, aryl, heteroaryl, halogen, hydroxy, alkoxy, aryloxy, amino, alkylamino, arylamino, sulfido, alkylsulfido, arylsulfido, phophino, alkylphosphino or arylphosphino and p and q are integers between 0 and 2.

29.   The light emitting device of claim 28 wherein J is selected from the group consisting of H, Ag, Zn, Al, B, Ga, In, Cd, Hg, Cu, Au.

30.   The light emitting device of claim 27, wherein X and Y are heterocycles.

31.   The light emitting device of claim 30 wherein X and Y are pyrazoles.

32.   The light emitting device of claim 28, wherein J is boron.

33.   The light emitting device of claim 32, wherein X and Y are both pyrazoles .

34.   The light emitting device of claim 33 wherein R' is pyrazole, b is equal to 0 and a is equal to 2.

35.   The light emitting device of claim 28 wherein R' is selected from the group consisting of bidentate alkyl, aryl and carboxyl ligands and chelating coordination ligands, b is equal to 0 and a is equal to 1.

36.   The light emitting device of claim 27 wherein R' and R" are selected from the group consisting of alkyls, aryls, and pyrazoles and p and q are each equal to 1.

37.   The light emitting device of claim 27, wherein Z is hydrogen.

38.   The light emitting device of claim 37, wherein X and Y are pyrazoles.

39.   The light emitting device of claim 27, wherein the heavy metal is selected from the group consisting of Ir, Pt, Pd, Rh, Re, Os, Tl, Pb, Bi, In, Sn, Sb, Te, Ag, Au.

40.   The light emitting device of claim 39 wherein the heavy metal is Ir.

41.   The light emitting device of claim 39 wherein the heavy metal is Pt.

42.   The light emitting device of claim 27 wherein at least one of X and Y is selected from the group consisting of OR, SR, NR_2, PR_2.

43.   The light emitting device of claim 49, wherein R is selected from the group consisting of H, alkyl, aryl, heteroaryl, halogen, alkoxy, amino, alkylamino, arylamino, sulfido, alkylsulfido, arylsulfido, phophino, alkylphosphino or arylphosphino.

Figure 1

200

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220

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210

Figure 2

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(54) Title: ORGANIC ELEMENT FOR ELECTROLUMINESCENT DEVICES

(57) Abstract: Disclosed is an electroluminescent device comprising a light-emitting layer containing a light emitting material that contains an organometallic complex comprising a metal selected from the group consisting of Pt, Pd and Ir, and a tridentate (N^C^N) ligand, wherein the tridentate (N^C^N) ligand represents a ligand that coordinates to the metal through a nitrogen donor bond, a carbon-metal bond, and a nitrogen donor bond, in that order, wherein at least one of the nitrogen donors is part of an aromatic ring or an imine group. The invention also includes a display or room lighting device employing the device of the invention and a process of emitting light from the device of the invention. The device of the invention provides good luminance efficiency.

ORGANIC ELEMENT FOR ELECTROLUMINESCENT DEVICES

FIELD OF THE INVENTION

This invention relates to an organic light emitting diode (OLED) electroluminescent (EL) device comprising a light-emitting layer containing an

5   organometallic complex that provides desirable electroluminescent properties.

BACKGROUND OF THE INVENTION

While organic electroluminescent (EL) devices have been known for over two decades, their performance limitations have represented a barrier to many desirable applications. In simplest form, an organic EL device is comprised

10   of an anode for hole injection, a cathode for electron injection, and an organic medium sandwiched between these electrodes to support charge recombination that yields emission of light. These devices are also commonly referred to as organic light-emitting diodes, or OLEDs. Representative of earlier organic EL devices are Gurnee et al. U.S. Pat. No. 3,172,862, issued Mar. 9, 1965; Gurnee

15   U.S. Pat. No. 3,173,050, issued Mar. 9, 1965; Dresner, "Double Injection Electroluminescence in Anthracene", RCA Review, Vol. 30, pp. 322-334, 1969; and Dresner U.S. Pat. No. 3,710,167, issued Jan. 9, 1973. The organic layers in these devices, usually composed of a polycyclic aromatic hydrocarbon, were very thick (much greater than 1 μm). Consequently, operating voltages were very high,

20   often >100V.

More recent organic EL devices include an organic EL element consisting of extremely thin layers (e.g. <1.0 μm) between the anode and the cathode. Herein, the term "organic EL element" encompasses the layers between the anode and cathode electrodes. Reducing the thickness lowered the resistance

25   of the organic layer and has enabled devices that operate much lower voltage. In a basic two-layer EL device structure, described first in US 4,356,429, one organic layer of the EL element adjacent to the anode is specifically chosen to transport holes, therefore, it is referred to as the hole-transporting layer, and the other organic layer is specifically chosen to transport electrons, referred to as the

electron-transporting layer. Recombination of the injected holes and electrons within the organic EL element results in efficient electroluminescence.

There have also been proposed three-layer organic EL devices that contain an organic light-emitting layer (LEL) between the hole-transporting layer

5 and electron-transporting layer, such as that disclosed by Tang et al [*J. Applied Physics*, Vol. 65, Pages 3610-3616, 1989]. The light-emitting layer commonly consists of a host material doped with a guest material Still further, there has been proposed in US 4,769,292 a four-layer EL element comprising a hole-injecting layer (HIL), a hole-transporting layer (HTL), a light-emitting layer (LEL) and an

10 electron transport/injection layer (ETL). These structures have resulted in improved device efficiency.

Many emitting materials that have been described as useful in an OLED device emit light from their excited singlet state by fluorescence. The excited singlet state is created when excitons formed in an OLED device transfer

15 their energy to the excited state of the dopant. However, it is generally believed that only 25% of the excitons created in an EL device are singlet excitons. The remaining excitons are triplet, which cannot readily transfer their energy to the singlet excited state of a dopant. This results in a large loss in efficiency since 75% of the excitons are not used in the light emission process.

20 Triplet excitons can transfer their energy to a dopant if it has a triplet excited state that is low enough in energy. If the triplet state of the dopant is emissive it can produce light by phosphorescence, wherein phosphorescence is a luminescence involving a change of spin state between the excited state and the ground state. In many cases singlet excitons can also transfer their energy to

25 lowest singlet excited state of the same dopant. The singlet excited state can often relax, by an intersystem crossing process, to the emissive triplet excited state. Thus, it is possible, by the proper choice of host and dopant, to collect energy from both the singlet and triplet excitons created in an OLED device and to produce a very efficient phosphorescent emission.

30

One class of useful phosphorescent materials are transition metal complexes having a triplet excited state. For example, *fac*-tris(2-phenylpyridinato-N,$C^{2'}$)iridium(III) (Ir(ppy)$_3$) strongly emits green light from a triplet excited state owing to the large spin-orbit coupling of the heavy atom and to

5 the lowest excited state which is a charge transfer state having a Laporte allowed (orbital symmetry) transition to the ground state (K.A. King, P.J. Spellane, and R.J. Watts, *J. Am. Chem. Soc.*, **107**, 1431 (1985), M.G. Colombo, T.C. Brunold, T. Reidener, H.U. Gudel, M. Fortsch, and H.-B. Burgi, *Inorg. Chem.*, **33**, 545 (1994) Small-molecule, vacuum-deposited OLEDs having high efficiency have also been

10 demonstrated with Ir(ppy)$_3$ as the phosphorescent material and 4,4'-N,N'-dicarbazole-biphenyl (CBP) as the host (M.A. Baldo, S. Lamansky, P.E. Burrows, M.E. Thompson, S.R. Forrest, *Appl. Phys. Lett.*, **75**, 4 (1999), T. Tsutsui, M.-J. Yang, M. Yahiro, K. Nakamura, T. Watanabe, T. Tsuji, Y. Fukuda, T. Wakimoto, S. Miyaguchi, *Jpn. J. Appl. Phys.*, **38**, L1502 (1999)).

15 Another class of phosphorescent materials include compounds having interactions between atoms having d^{10} electron configuration, such as Au$_2$(dppm)Cl$_2$ (dppm = bis(diphenylphosphino)methane) (Y. Ma et al, *Appl. Phys. Lett.*, **74**, 1361 (1998)). Still other examples of useful phosphorescent materials include coordination complexes of the trivalent lanthanides such as Tb^{3+} and

20 Eu^{3+}(J. Kido et al, *Appl. Phys. Lett.*, **65**, 2124 (1994)). While these latter phosphorescent compounds do not necessarily have triplets as the lowest excited states, their optical transitions do involve a change in spin state of 1 and thereby can harvest the triplet excitons in OLED devices.

Although many phosphorescent Ir complexes have been described

25 as useful in an EL device, Pt-based organometallic complexes have not been examined as extensively. Some Pt phosphorescent complexes include cyclometallated Pt(II) complexes such as cis-bis(2-phenylpyridinato-N,$C^{2'}$)platinum(II), cis-bis(2-(2'-thienyl)pyridinato-N,$C^{3'}$) platinum(II), cis-bis(2-(2'-thienyl)quinolinato-N,$C^{5'}$) platinum(II), or (2-(4,6-diflourophenyl)pyridinato-

30 NC2') platinum (II) acetylacetonate. Pt(II) porphyrin complexes such as

2,3,7,8,12,13,17,18-octaethyl-21H, 23H-porphine platinum(II) are reported in US
6,048,630 as useful phosphorescent materials in an electroluminescent device
although they did not give a very high luminance yield. Recently, C. Che, W. Lu,
and M. Chan reported organometallic light-emitting materials based on (C^N^N)
5   tridentate cyclometalated Pt(II) arylacetylides. (US 2002/0179885 and references
cited therein)

Complexes of a tridentate (N^C^N) ligand have been examined,
wherein the tridentate (N^C^N) ligand represents a ligand that coordinates to the
metal through a nitrogen donor bond, a carbon-metal bond, and a nitrogen donor
10 bond, in that order, wherein at least one of the nitrogen donors is part of an
aromatic ring or an imine group (for example, see D. Cardenas, A. Echavarren, A.
M. Ramirez de Arellano, Organometallics (1999), **18**, 3337 (1999) and
references cited therein). Nevertheless, there continues a need for additional
phosphorescent emitters that exhibit good luminance efficiency in
15 electroluminescent devices.

SUMMARY OF THE INVENTION

The invention provides an electroluminescent device comprising a
light-emitting layer containing a light emitting material that contains an
organometallic complex comprising a metal selected from the group consisting of
20 Pt, Pd and Ir, and a tridentate (N^C^N) ligand, wherein the tridentate (N^C^N)
ligand represents a ligand that coordinates to the metal through a nitrogen donor
bond, a carbon-metal bond, and a nitrogen donor bond, in that order, wherein at
least one of the nitrogen donors is part of an aromatic ring or an imine group. The
invention also includes a display or room lighting device employing the device of
25 the invention.

The device of the invention provides good luminance efficiency.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a cross-section of a typical OLED device in which
this invention may be used.

30

DETAILED DESCRIPTION OF THE INVENTION

The invention is generally summarized above. The organometallic complex of the invention comprises a metal consisting of Pt, Pd or Ir; more desirably the metal is Pt. The metal forms a complex with a tridentate (N^C^N)

5   ligand, wherein the tridentate (N^C^N) ligand represents a ligand that coordinates to the metal through a nitrogen donor bond, a carbon bond, and a nitrogen donor bond, in that order, wherein at least one of the nitrogen donors is part of an aromatic ring or an imine group. The complex may be present in a compound containing two or more complexes. Examples of suitable ligands are shown

10   below. Desirably, both of the nitrogen donors are part of an aromatic ring.
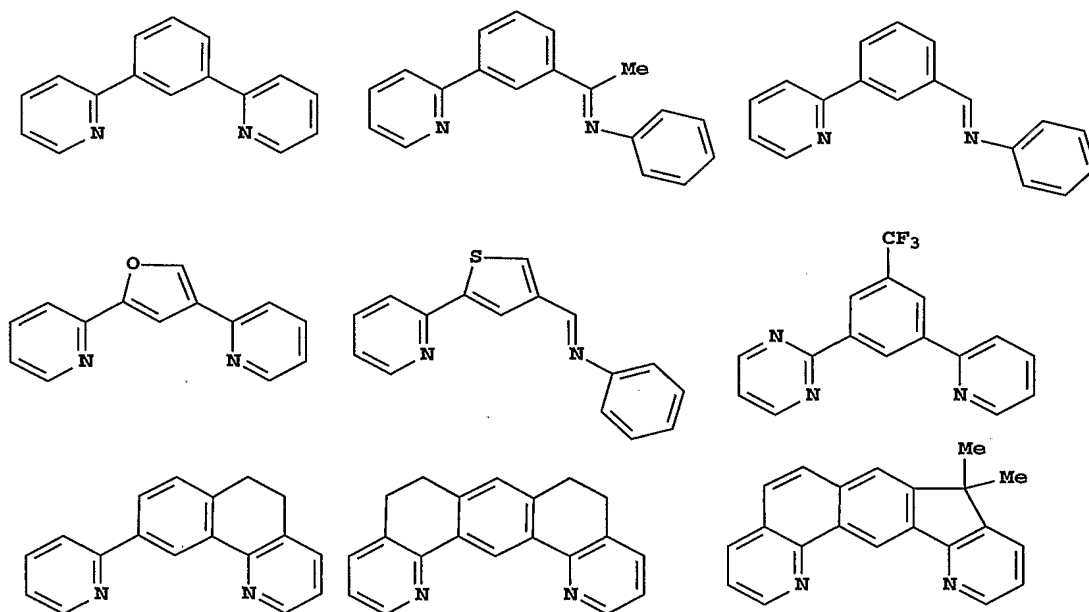
In one suitable embodiment, the tridentate organometallic complex

15   can be incorporated into a polymer light emitting diode (PLED) device. For example, the organometallic complex can be part of the main chain of a polymer, the side chain, or intermixed with a polymer in such a device.

In one desirable embodiment the organometallic complex can be represented by Formula (1a),
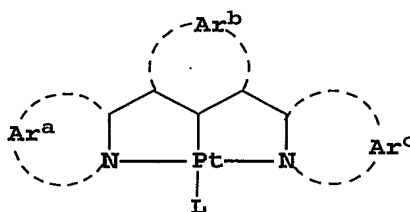
20

(1a)

wherein:

Ar^a, Ar^b, and Ar^c independently represent the atoms necessary to

form a five or six-membered aromatic ring, which may be further substituted

including substitution by fused rings. The term 'aromatic rings' includes aromatic

rings that have heteroatoms present in the ring, see for example, J. March,

Advanced Organic Chemistry, Chapter 2 (1985, publisher John Wiley & Sons,

New York, NY). For example, Ar^b can represent the atoms necessary to form

groups such as benzene ring groups, thiophene ring groups, or furan ring groups.

Likewise, Ar^a and Ar^c can represent the atoms necessary to form groups such as

pyridine ring groups, quinoline ring groups, isoquinoline ring groups, and indole

ring groups as examples. In one desirable embodiment, Ar^b represents a benzene

ring group and Ar^a and Ar^c independently represent pyridine ring groups.

L represents an anionic ligand having a negative charge and formed

by loss of hydrogen from the parent compound LH. In the L-metal bond, more of

the electron density is localized on L, the ligand. For example, L can represent

halogen, that is fluoride, chloride, bromide, or iodide. L can also be chosen so that

it forms a carbon-metal bond in the organometallic complex, for example, L can

represent a cyanide, an alkynyl group, an alkenyl group, an aryl group, or an alkyl

group. Illustrative examples of such L groups are shown below.
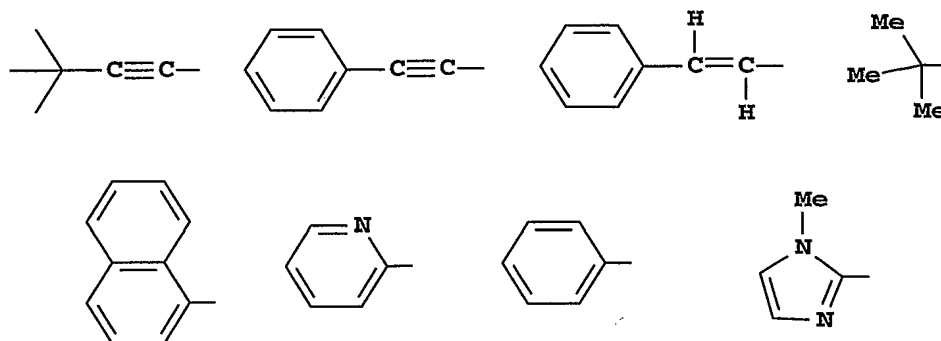
L can also represent RX, wherein X forms a bond to the metal (Pt,
Pd or Ir) and wherein X represents N, O, S, or Se, and R represents a substituent.
For example, R can represent an aryl group or an alkyl group or a carbonyl group
or sulfonyl group. Suitable examples of groups represented by RX are a
thiocyanate, alkoxide or aryloxide groups, alkyl sulfide or aryl sulfide groups, a
carboxlate group or sulfonate group, for example, acetate, trifluoroacetate,
tosylate, triflate. Illustrative examples of RX are also given below.
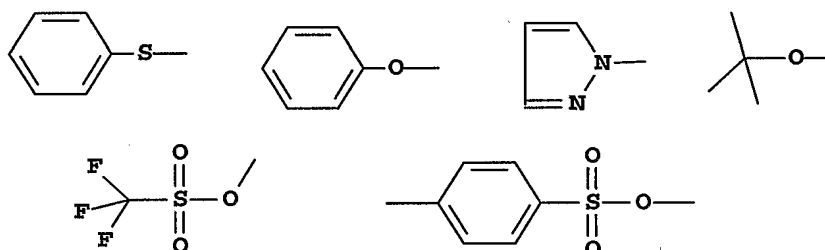
In one desirable embodiment the organometallic complex of the
invention can be represented by Formula (1b).

(1b)
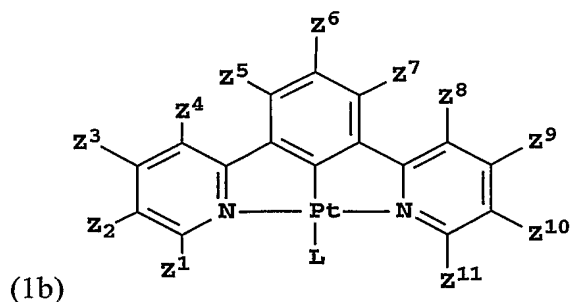
$Z^1 - Z^{11}$ of formula (1b) represent hydrogen or independently selected substituent groups, provided that adjacent substituent groups can combine to form rings. Examples of substituents are phenyl groups, alkyl groups such as methyl groups or t-butyl groups. Z^4 and Z^5 as well as Z^7 and Z^8 can also combine to form rings, for example, a 6-membered saturated ring or a 6-membered aromatic ring. L represents ian anionic ligand.

In another desirable embodiment the organometallic complex can be represented by Formula (1c).

(1c)
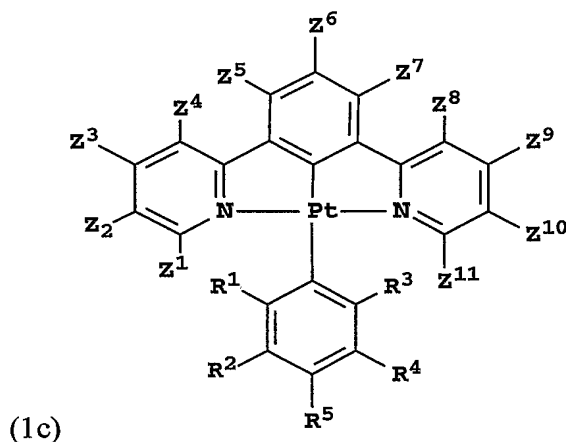
As described above, $Z^1 - Z^{11}$ represent hydrogen or independently selected substituent groups, provided that adjacent substituent groups can combine to form rings, and provided that Z^4 and Z^5 as well as Z^7 and Z^8 can combine to form rings. L represents is an anionic ligand.

$R^1 - R^5$ represent hydrogen or independently selected substituents, provided that adjacent substituents may combine to form a ring group, which may be further substituted including substitution by fused rings. For example, R^1 and R^3 can independently represent groups such as methyl groups or isopropyl groups.

R^1 and R^2, and R^3 and R^4 can combine to form rings such as benzene ring groups or tolyl ring groups.

Synthetic Method

5   Synthesis of the emitting materials useful in the invention may be accomplished by preparing the organic ligand and then using a metal to complex the ligand and form the organometallic compound. Suitable tridentate ligands and their metal complexes can be prepared by various literature methods, for example, see M. Beley, J. Collin, J. Sauvage, *Inorg.Chem.*, **32**, 4539(1993), M. Beley, J.

10   Collin, R. Louis,B. Metz, J.Sauvage, *J. Am. Chem. Soc.*, **113**, 8521 (1991), D. Cardenas, A. Echavarren, Antonio M.; Ramirez de Arellano, M. Carmen, *Organometallics*, **18**, 3337 (1999), and M. Sindkhedkar, H. Mulla, M. Wurth, A. Cammers-Goodwin, *Tetrahedron*, **57**, 2991(2001). For example, one synthetic method involves reaction of a bromo compound (Rxn-1, wherein Ar^w represents

15   the atoms necessary to complete a five or six-membered aromatic ring group) with butyllithium at low temperature, followed by addition of zinc chloride. This affords a zinc intermediate. This intermediate need not be isolated; after addition of tetrakis(triphenylphosphine) palladium , it can be reacted further with 0.5 equivalents of a dibromo compound to afford a tridentate ligand (Rxn-2, wherein

20   Ar^y represents the atoms necessary to complete a five or six-membered aromatic ring group). Alternatively, two equivalents of a bromoheterocyclic compound can be reacted with a diboron intermediate to afford a tridentate ligand (Rxn-3). Unsymmetrical ligands can be made by reacting one equivalent of a bromoheterocyclic compound with a diboron intermediate to afford a bidentate

25   ligand and this ligand can be isolated and then reacted further with another bromoheterocyclic compound to obtain the tridentate ligand (Rxn-4 and Rxn-5, wherein Ar^z represents the atoms necessary to complete a five or six-membered aromatic ring group). The ligands can be isolated and purified by various methods, including column chromatography.

30   Reaction of the tridentate ligand with a metal salt, for example

potassium tetrachloroplatinate, affords the desired organometallic complex (Rxn-6). The chloro group in the organometallic complex can be replaced by other ligands. For example, chloride can be replaced by reaction of the complex with an aryl lithium or zinc salt or a copper catalyzed reaction with an acetlylene

5   substituted group (Rxn-7 and Rxn-8, wherein Ar^s represents a five or six-membered aromatic ring group, R^w is a substituent group).
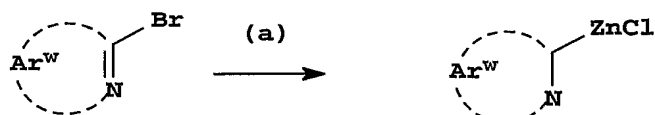
(a) THF, BuLi, -78°C, $ZnCl_2$

Rxn-1
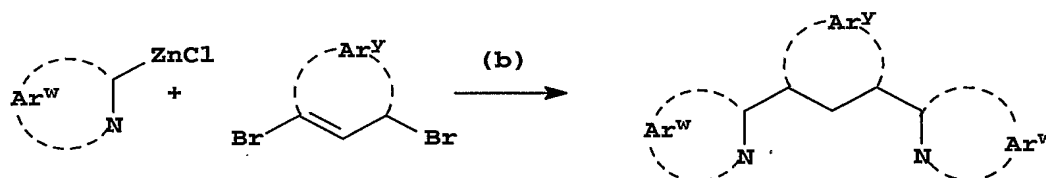
(b) $Pd(PPh_3)_4$

Rxn-2
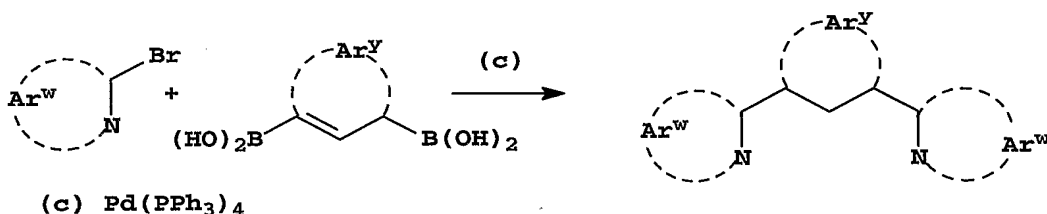
(c) $Pd(PPh_3)_4$

Rxn-3

(d) $Pd(PPh_3)_4$

Rxn-4

(e) Pd(PPh₃)₄

Rxn-5

(f) HOAc, K₂PtCl₄

5   Rxn-6

(g) Aryllithum or zinc salt

Rxn-7

10

(h) CuI/Et₃N
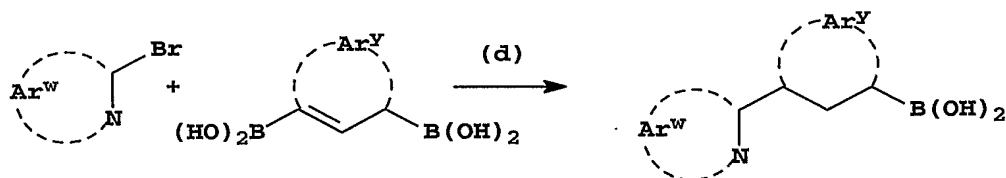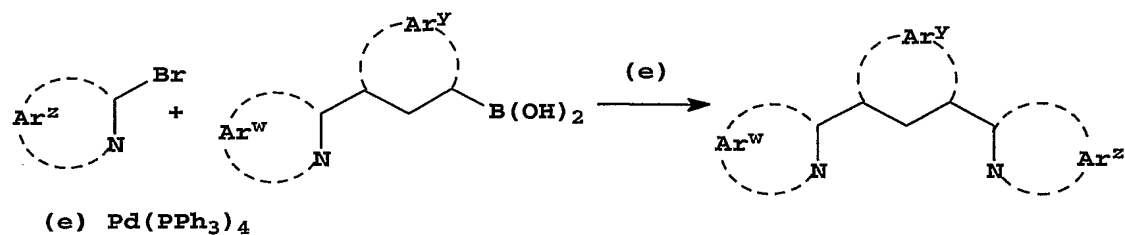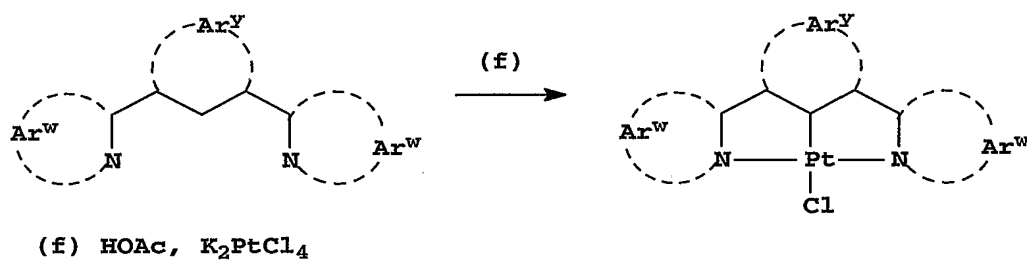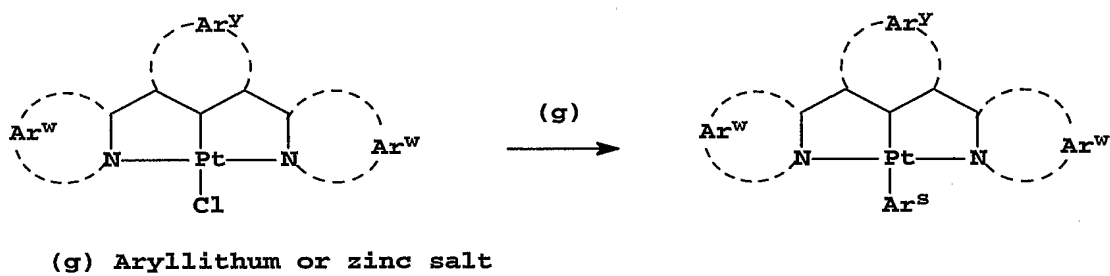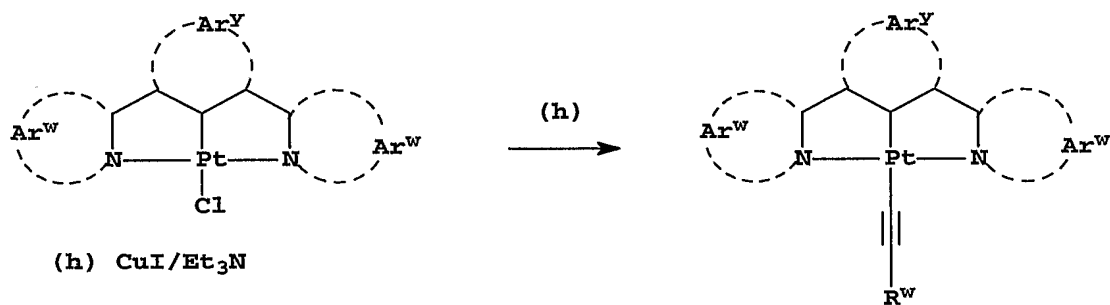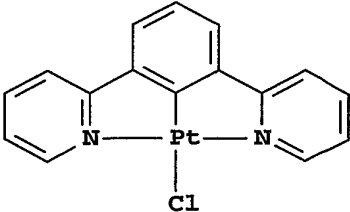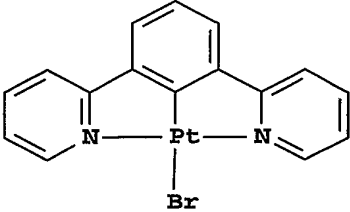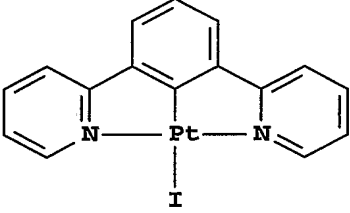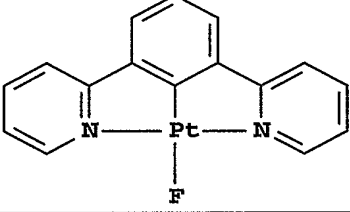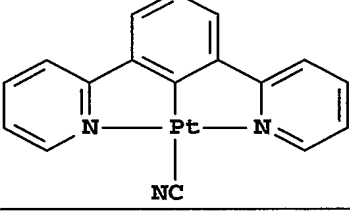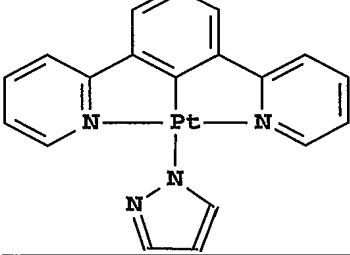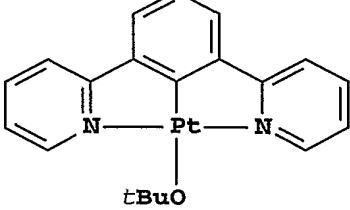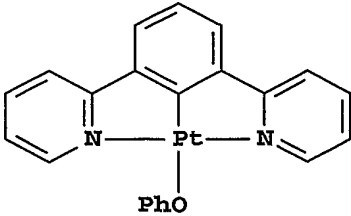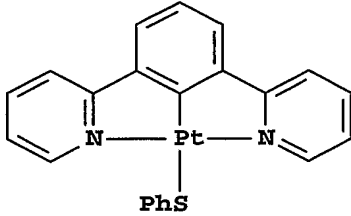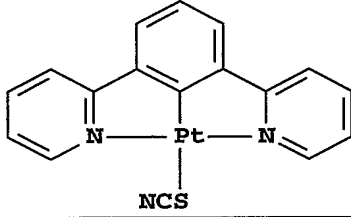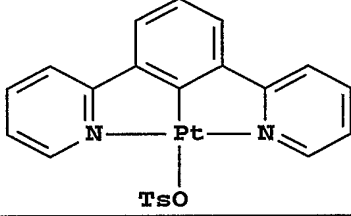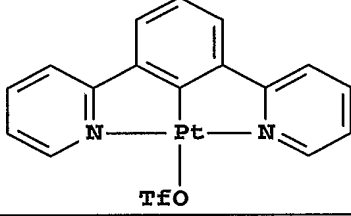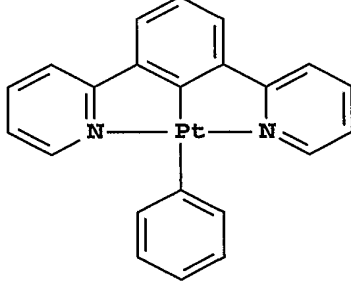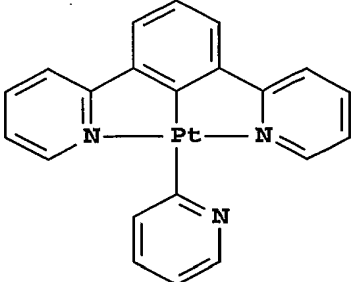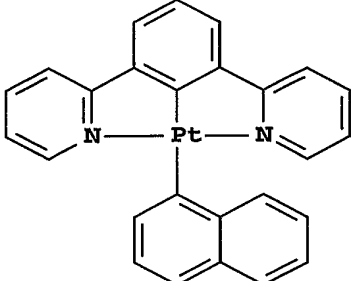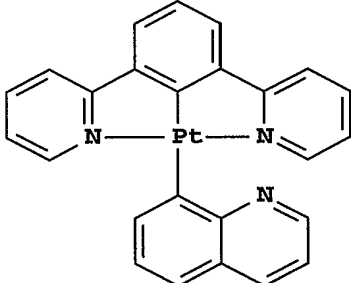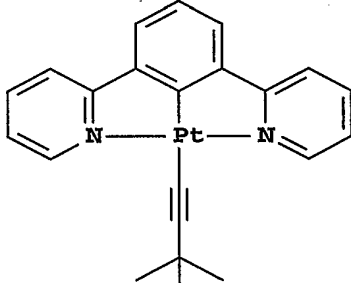
Rxn-8
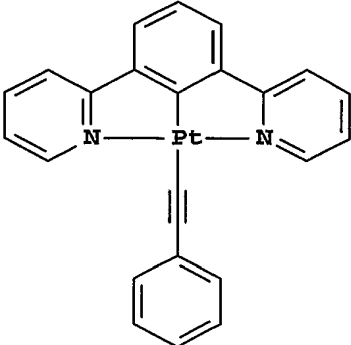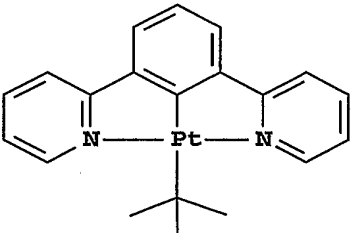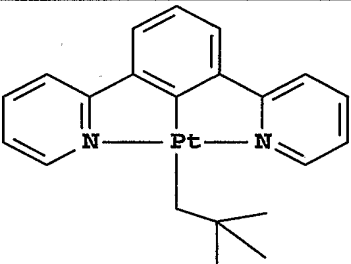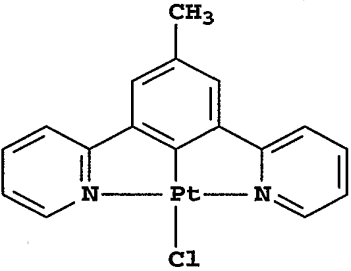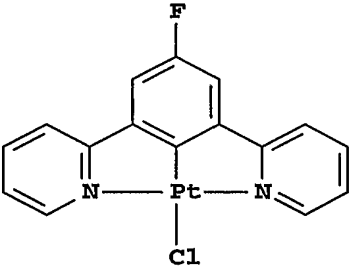
Illustrative examples of complexes of Formula (1) useful in the present invention are the following:

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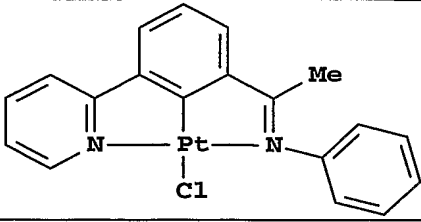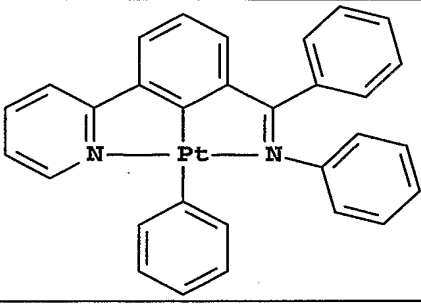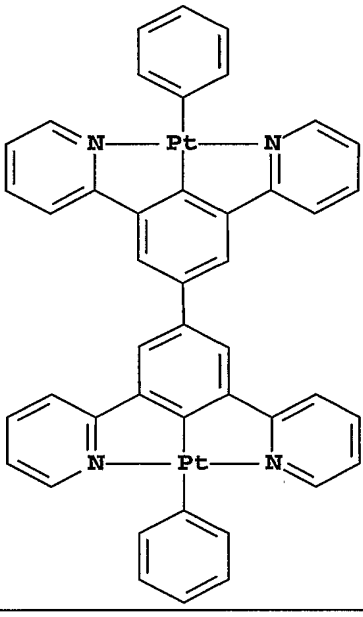
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| Inv-56 | |
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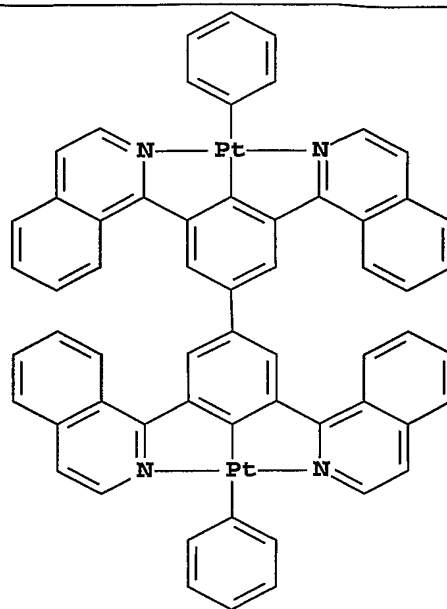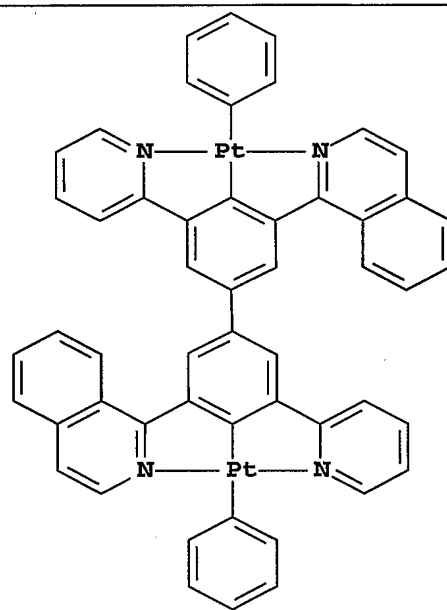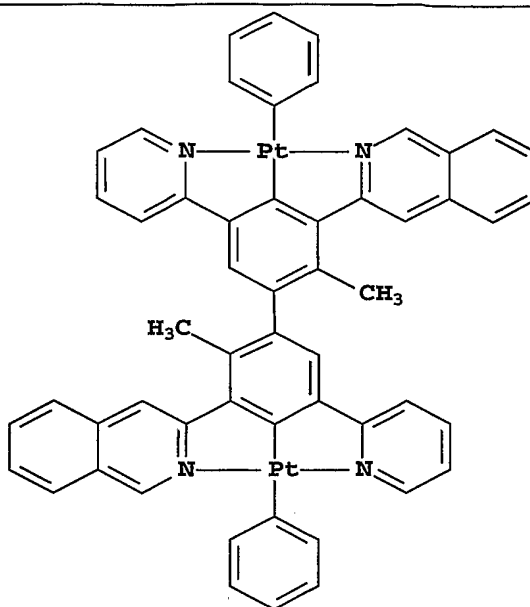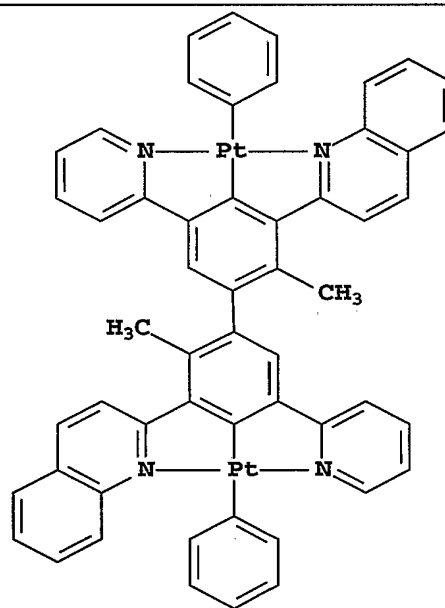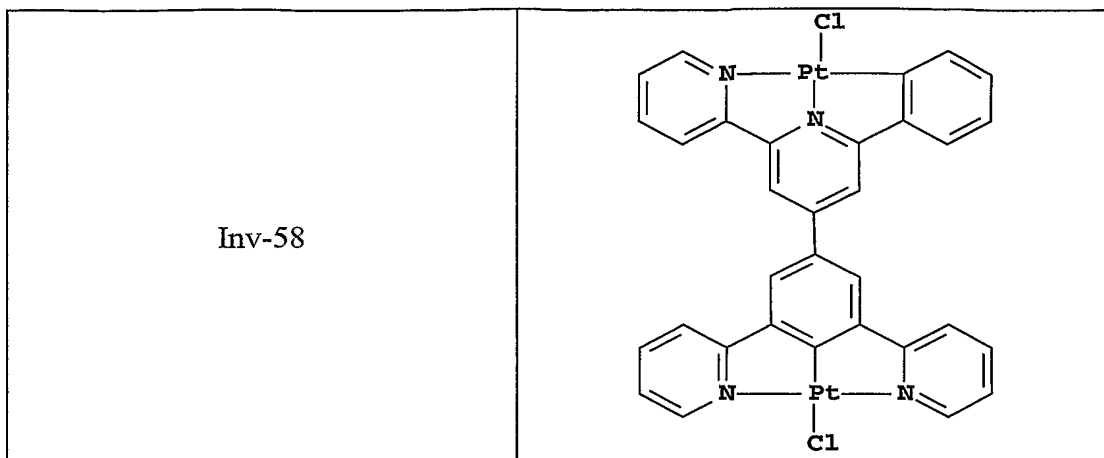
Unless otherwise specifically stated, use of the term "substituted" or "substituent" means any group or atom other than hydrogen. Unless otherwise

5   provided, when a group (including a compound or complex) containing a substitutable hydrogen is referred to, it is also intended to encompass not only the unsubstituted form, but also form further substituted derivatives with any substituent group or groups as herein mentioned, so long as the substituent does not destroy properties necessary for utility. Suitably, a substituent group may be

10   halogen or may be bonded to the remainder of the molecule by an atom of carbon, silicon, oxygen, nitrogen, phosphorous, sulfur, selenium, or boron. The substituent may be, for example, halogen, such as chloro, bromo or fluoro; nitro; hydroxyl; cyano; carboxyl; or groups which may be further substituted, such as alkyl, including straight or branched chain or cyclic alkyl, such as methyl,

15   trifluoromethyl, ethyl, t-butyl, 3-(2,4-di-t-pentylphenoxy) propyl, and tetradecyl; alkenyl, such as ethylene, 2-butene; alkoxy, such as methoxy, ethoxy, propoxy, butoxy, 2-methoxyethoxy, sec-butoxy, hexyloxy, 2-ethylhexyloxy, tetradecyloxy, 2-(2,4-di-t-pentylphenoxy)ethoxy, and 2-dodecyloxyethoxy; aryl such as phenyl, 4-t-butylphenyl, 2,4,6-trimethylphenyl, naphthyl; aryloxy, such as phenoxy, 2-

20   methylphenoxy, alpha- or beta-naphthyloxy, and 4-tolyloxy; carbonamido, such as acetamido, benzamido, butyramido, tetradecanamido, alpha-(2,4-di-t-pentyl-phenoxy)acetamido, alpha-(2,4-di-t-pentylphenoxy)butyramido, alpha-(3-pentadecylphenoxy)-hexanamido, alpha-(4-hydroxy-3-t-butylphenoxy)-

tetradecanamido, 2-oxo-pyrrolidin-1-yl, 2-oxo-5-tetradecylpyrrolin-1-yl, N-methyltetradecanamido, N-succinimido, N-phthalimido, 2,5-dioxo-1-oxazolidinyl, 3-dodecyl-2,5-dioxo-1-imidazolyl, and N-acetyl-N-dodecylamino, ethoxycarbonylamino, phenoxycarbonylamino, benzyloxycarbonylamino,

5   hexadecyloxycarbonylamino, 2,4-di-t-butylphenoxycarbonylamino, phenylcarbonylamino, 2,5-(di-t-pentylphenyl)carbonylamino, p-dodecyl-phenylcarbonylamino, p-tolylcarbonylamino, N-methylureido, N,N-dimethylureido, N-methyl-N-dodecylureido, N-hexadecylureido, N,N-dioctadecylureido, N,N-dioctyl-N'-ethylureido, N-phenylureido, N,N-

10   diphenylureido, N-phenyl-N-p-tolylureido, N-(m-hexadecylphenyl)ureido, N,N-(2,5-di-t-pentylphenyl)-N'-ethylureido, and t-butylcarbonamido; sulfonamido, such as methylsulfonamido, benzenesulfonamido, p-tolylsulfonamido, p-dodecylbenzenesulfonamido, N-methyltetradecylsulfonamido, N,N-dipropyl-sulfamoylamino, and hexadecylsulfonamido; sulfamoyl, such as N-

15   methylsulfamoyl, N-ethylsulfamoyl, N,N-dipropylsulfamoyl, N-hexadecylsulfamoyl, N,N-dimethylsulfamoyl, N-[3-(dodecyloxy)propyl]sulfamoyl, N-[4-(2,4-di-t-pentylphenoxy)butyl]sulfamoyl, N-methyl-N-tetradecylsulfamoyl, and N-dodecylsulfamoyl; carbamoyl, such as N-methylcarbamoyl, N,N-dibutylcarbamoyl, N-octadecylcarbamoyl, N-[4-(2,4-di-t-

20   pentylphenoxy)butyl]carbamoyl, N-methyl-N-tetradecylcarbamoyl, and N,N-dioctylcarbamoyl; acyl, such as acetyl, (2,4-di-t-amylphenoxy)acetyl, phenoxycarbonyl, p-dodecyloxyphenoxycarbonyl methoxycarbonyl, butoxycarbonyl, tetradecyloxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, 3-pentadecyloxycarbonyl, and dodecyloxycarbonyl; sulfonyl, such as

25   methoxysulfonyl, octyloxysulfonyl, tetradecyloxysulfonyl, 2-ethylhexyloxysulfonyl, phenoxysulfonyl, 2,4-di-t-pentylphenoxysulfonyl, methylsulfonyl, octylsulfonyl, 2-ethylhexylsulfonyl, dodecylsulfonyl, hexadecylsulfonyl, phenylsulfonyl, 4-nonylphenylsulfonyl, and p-tolylsulfonyl; sulfonyloxy, such as dodecylsulfonyloxy, and hexadecylsulfonyloxy; sulfinyl, such

30   as methylsulfinyl, octylsulfinyl, 2-ethylhexylsulfinyl, dodecylsulfinyl, hexadecylsulfinyl, phenylsulfinyl, 4-nonylphenylsulfinyl, and p-tolylsulfinyl; thio,

such as ethylthio, octylthio, benzylthio, tetradecylthio, 2-(2,4-di-t-
pentylphenoxy)ethylthio, phenylthio, 2-butoxy-5-t-octylphenylthio, and p-
tolylthio; acyloxy, such as acetyloxy, benzoyloxy, octadecanoyloxy, p-
dodecylamidobenzoyloxy, N-phenylcarbamoyloxy, N-ethylcarbamoyloxy, and

5   cyclohexylcarbonyloxy; amine, such as phenylanilino, 2-chloroanilino,
diethylamine, dodecylamine; imino, such as 1 (N-phenylimido)ethyl, N-
succinimido or 3-benzylhydantoinyl; phosphate, such as dimethylphosphate and
ethylbutylphosphate; phosphite, such as diethyl and dihexylphosphite; a
heterocyclic group, a heterocyclic oxy group or a heterocyclic thio group, each of

10   which may be substituted and which contain a 3 to 7 membered heterocyclic ring
composed of carbon atoms and at least one hetero atom selected from the group
consisting of oxygen, nitrogen, sulfur, phosphorous, or boron. such as 2-furyl, 2-
thienyl, 2-benzimidazolyloxy or 2-benzothiazolyl; quaternary ammonium, such as
triethylammonium; quaternary phosphonium, such as triphenylphosphonium; and

15   silyloxy, such as trimethylsilyloxy.

       If desired, the substituents may themselves be further substituted
one or more times with the described substituent groups. The particular
substituents used may be selected by those skilled in the art to attain the desired
desirable properties for a specific application and can include, for example,

20   electron-withdrawing groups, electron-donating groups, and steric groups. When a
molecule may have two or more substituents, the substituents may be joined
together to form a ring such as a fused ring unless otherwise provided. Generally,
the above groups and substituents thereof may include those having up to 48
carbon atoms, typically 1 to 36 carbon atoms and usually less than 24 carbon

25   atoms, but greater numbers are possible depending on the particular substituents
selected.

       Suitably, the light-emitting layer of the OLED device comprises a
host material and one or more guest materials for emitting light. At least one of the
guest materials is suitably a phosphorescent complex comprising a ring system of

30   Formula 1a. The light-emitting guest material(s) is usually present in an amount
less than the amount of host materials and is typically present in an amount of up

to 15 wt % of the host, more typically from 0.1-10.0 wt % of the host   For
convenience, the phosphorescent complex guest material may be referred to herein
as a phosphorescent material. The phosphorescent material of Formula 1a is
preferably a low molecular weight compound, but it may also be an oligomer or a
5   polymer having a main chain or a side chain of repeating units having the moiety
represented by Formula 1a. It may be provided as a discrete material dispersed in
the host material, or it may be bonded in some way to the host material, for
example, covalently bonded into a polymeric host.

10   Host Materials for Phosphorescent Materials

              Suitable host materials should be selected so that the triplet exciton
can be transferred efficiently from the host material to the phosphorescent
material. For this transfer to occur, it is a highly desirable condition that the
excited state energy of the phosphorescent material be lower than the difference in
15   energy between the lowest triplet state and the ground state of the host. However,
the band gap of the host should not be chosen so large as to cause an unacceptable
increase in the drive voltage of the OLED. Suitable host materials are described in
WO 00/70655 A2; 01/39234 A2; 01/ 93642 A1; 02/074015 A2; 02/15645 A1, and
US 20020117662. Suitable hosts include certain aryl amines, triazoles, indoles and
20   carbazole compounds. Examples of desirable hosts are 4,4'-N,N'-dicarbazole-
biphenyl (CBP), 2,2'-dimethyl-4,4'-N,N'-dicarbazole-biphenyl, m-(N,N'-
dicarbazole)benzene, and poly(N-vinylcarbazole), including their derivatives.

              Desirable host materials are capable of forming a continuous film.
The light-emitting layer may contain more than one host material in order to
25   improve the device's film morphology, electrical properties, light emission
efficiency, and lifetime. The light emitting layer may contain a first host material
that has good hole-transporting properties, and a second host material that has
good electron-transporting properties.

30

Other Phosphorescent Materials

        Phosphorescent materials of Formula 1a may be used in combination with other phosphorescent materials, either in the same or different layers. Some other phosphorescent materials are described in WO 00/57676, WO

5   00/70655, WO 01/41512 A1, WO 02/15645 A1, US 2003/0017361 A1, WO 01/93642 A1, WO 01/39234 A2, US 6,458,475 B1, WO 02/071813 A1, US 6,573,651 B2, US 2002/0197511 A1, WO 02/074015 A2, US 6,451,455 B1, US 2003/ 0072964 A1, US 2003 / 0068528 A1, US 6,413,656 B1, US 6,515,298 B2, US 6,451,415 B1, US 6,097,147, US 2003/0124381 A1, US 2003/0059646 A1,

10   US 2003/0054198 A1, EP 1 239 526 A2, EP 1 238 981 A2, EP 1 244 155 A2, US 2002/0100906 A1, US 2003 / 0068526 A1, US 2003/0068535 A1, JP 2003073387A, JP 2003 073388A, US 2003/0141809 A1, US 2003/0040627 A1, JP 2003059667A, JP 2003073665A, and US 2002/0121638 A1.

        The emission wavelengths of cyclometallated Ir(III) complexes of

15   the type IrL_3 and IrL_2L', such as the green-emitting *fac*-tris(2-phenylpyridinato-N,$C^{2'}$)Iridium(III) and bis(2-phenylpyridinato-N,$C^{2'}$)Iridium(III)(acetylacetonate) may be shifted by substitution of electron donating or withdrawing groups at appropriate positions on the cyclometallating ligand L, or by choice of different heterocycles for the cyclometallating ligand L. The emission wavelengths may

20   also be shifted by choice of the ancillary ligand L'. Examples of red emitters are the bis(2-(2'-benzothienyl)pyridinato-N,$C^{3'}$)Iridium(III)(acetylacetonate) and tris(1-phenylisoquinolinato-N,C)Iridium(III). A blue-emitting example is bis(2-(4,6-diflourophenyl)-pyridinato-N,$C^{2'}$)Iridium(III)(picolinate).

        Red electrophosphorescence has been reported, using bis(2-(2'-

25   benzo[4,5-a]thienyl)pyridinato-N, C^{3}) iridium (acetylacetonate) [Btp$_2$Ir(acac)] as the phosphorescent material (Adachi, C., Lamansky, S., Baldo, M. A., Kwong, R. C., Thompson, M. E., and Forrest, S. R., *App. Phys. Lett.*, **78**, 1622-1624 (2001).

        Still other examples of useful phosphorescent materials include coordination complexes of the trivalent lanthanides such as Tb^{3+} and Eu^{3+}(J. Kido

30   et al, *Appl. Phys. Lett.*, **65**, 2124 (1994))

Blocking Layers

In addition to suitable hosts, an OLED device employing a
phosphorescent material often requires at least one exciton or hole blocking layers
to help confine the excitons or electron-hole recombination centers to the light-
emitting layer comprising the host and phosphorescent material. In one
embodiment, such a blocking layer would be placed between the electron-
transporting layer and the light-emitting layer – see Fig 1, layer **110**. In this case,
the ionization potential of the blocking layer should be such that there is an energy
barrier for hole migration from the host into the electron-transporting layer, while
the electron affinity should be such that electrons pass more readily from the
electron-transporting layer into the light-emitting layer comprising host and
phosphorescent material. It is further desired, but not absolutely required, that the
triplet energy of the blocking material be greater than that of the phosphorescent
material. Suitable hole-blocking materials are described in WO 00/70655A2 and
WO 01/93642 A1. Two examples of useful materials are bathocuproine (BCP) and
bis(2-methyl-8-quinolinolato)(4-phenylphenolato)Aluminum(III) (BAlQ). Metal
complexes other than Balq are also known to block holes and excitons as
described in US 20030068528. US 20030175553 A1 describes the use of fac-
tris(1-phenylpyrazolato-N,C 2)iridium(III) (Irppz) in an electron/exciton blocking
layer.

Embodiments of the invention can provide advantageous features
such as operating efficiency, higher luminance, color hue, low drive voltage, and
improved operating stability. Embodiments of the organometallic compounds
useful in the invention can provide a wide range of hues including those useful in
the emission of white light (directly or through filters to provide multicolor
displays).

General Device Architecture

The present invention can be employed in many OLED device
configurations using small molecule materials, oligomeric materials, polymeric
materials, or combinations thereof. These include very simple structures

comprising a single anode and cathode to more complex devices, such as passive
matrix displays comprised of orthogonal arrays of anodes and cathodes to form
pixels, and active-matrix displays where each pixel is controlled independently,
for example, with thin film transistors (TFTs).

5   There are numerous configurations of the organic layers wherein
the present invention can be successfully practiced. The essential requirements of
an OLED are an anode, a cathode, and an organic light-emitting layer located
between the anode and cathode. Additional layers may be employed as more fully
described hereafter.

10   A typical structure, especially useful for of a small molecule
device, is shown in FIG. 1 and is comprised of a substrate **101**, an anode **103**, a
hole-injecting layer **105**, a hole-transporting layer **107**, a light-emitting layer **109**, a
hole- or exciton-blocking layer **110**, an electron-transporting layer **111**, and a
cathode **113**. These layers are described in detail below. Note that the substrate

15   may alternatively be located adjacent to the cathode, or the substrate may actually
constitute the anode or cathode. The organic layers between the anode and cathode
are conveniently referred to as the organic EL element. Also, the total combined
thickness of the organic layers is desirably less than 500 nm.

The anode and cathode of the OLED are connected to a

20   voltage/current source through electrical conductors. The OLED is operated by
applying a potential between the anode and cathode such that the anode is at a
more positive potential than the cathode. Holes are injected into the organic EL
element from the anode and electrons are injected into the organic EL element at
the cathode. Enhanced device stability can sometimes be achieved when the

25   OLED is operated in an AC mode where, for some time period in the cycle, the
potential bias is reversed and no current flows. An example of an AC driven
OLED is described in US 5,552,678.

Substrate

The OLED device of this invention is typically provided over a

30   supporting substrate **101** where either the cathode or anode can be in contact with
the substrate. The electrode in contact with the substrate is conveniently referred

to as the bottom electrode. Conventionally, the bottom electrode is the anode, but this invention is not limited to that configuration. The substrate can either be light transmissive or opaque, depending on the intended direction of light emission. The light transmissive property is desirable for viewing the EL emission through the

5   substrate. Transparent glass or plastic is commonly employed in such cases. The substrate can be a complex structure comprising multiple layers of materials. This is typically the case for active matrix substrates wherein TFTs are provided below the OLED layers. It is still necessary that the substrate, at least in the emissive pixilated areas, be comprised of largely transparent materials such as glass or

10   polymers. For applications where the EL emission is viewed through the top electrode, the transmissive characteristic of the bottom support is immaterial, and therefore can be light transmissive, light absorbing or light reflective. Substrates for use in this case include, but are not limited to, glass, plastic, semiconductor materials, silicon, ceramics, and circuit board materials. Again, the substrate can

15   be a complex structure comprising multiple layers of materials such as found in active matrix TFT designs. It is necessary to provide in these device configurations a light-transparent top electrode.

Anode

            When the desired electroluminescent light emission (EL) is viewed

20   through the anode, the anode should be transparent or substantially transparent to the emission of interest. Common transparent anode materials used in this invention are indium-tin oxide (ITO), indium-zinc oxide (IZO) and tin oxide, but other metal oxides can work including, but not limited to, aluminum- or indium-doped zinc oxide, magnesium-indium oxide, and nickel-tungsten oxide. In

25   addition to these oxides, metal nitrides, such as gallium nitride, and metal selenides, such as zinc selenide, and metal sulfides, such as zinc sulfide, can be used as the anode. For applications where EL emission is viewed only through the cathode, the transmissive characteristics of the anode are immaterial and any conductive material can be used, transparent, opaque or reflective. Example

30   conductors for this application include, but are not limited to, gold, iridium, molybdenum, palladium, and platinum. Typical anode materials, transmissive or

otherwise, have a work function of 4.1eV or greater. Desired anode materials are commonly deposited by any suitable means such as evaporation, sputtering, chemical vapor deposition, or electrochemical means. Anodes can be patterned using well-known photolithographic processes. Optionally, anodes may be

5   polished prior to application of other layers to reduce surface roughness so as to minimize shorts or enhance reflectivity.

Cathode

When light emission is viewed solely through the anode, the cathode used in this invention can be comprised of nearly any conductive material.

10 Desirable materials have good film-forming properties to ensure good contact with the underlying organic layer, promote electron injection at low voltage, and have good stability. Useful cathode materials often contain a low work function metal (< 4.0 eV) or metal alloy. One useful cathode material is comprised of a Mg:Ag alloy wherein the percentage of silver is in the range of 1 to 20 %, as described in

15 U.S. Patent No. 4,885,221. Another suitable class of cathode materials includes bilayers comprising the cathode and a thin electron-injection layer (EIL) in contact with an organic layer (e.g., an electron transporting layer (ETL)) which is capped with a thicker layer of a conductive metal. Here, the EIL preferably includes a low work function metal or metal salt, and if so, the thicker capping layer does not

20 need to have a low work function. One such cathode is comprised of a thin layer of LiF followed by a thicker layer of Al as described in U.S. Patent No. 5,677,572. An ETL material doped with an alkali metal, for example, Li-doped Alq, is another example of a useful EIL. Other useful cathode material sets include, but are not limited to, those disclosed in U.S. Patent Nos. 5,059,861, 5,059,862, and

25 6,140,763.

When light emission is viewed through the cathode, the cathode must be transparent or nearly transparent. For such applications, metals must be thin or one must use transparent conductive oxides, or a combination of these materials. Optically transparent cathodes have been described in more detail in US

30 4,885,211, US 5,247,190, JP 3,234,963, US 5,703,436, US 5,608,287, US 5,837,391, US 5,677,572, US 5,776,622, US 5,776,623, US 5,714,838, US

5,969,474, US 5,739,545, US 5,981,306, US 6,137,223, US 6,140,763, US
6,172,459, EP 1 076 368, US 6,278,236, and US 6,284,3936. Cathode materials
are typically deposited by any suitable method such as evaporation, sputtering, or
chemical vapor deposition. When needed, patterning can be achieved through

5   many well known methods including, but not limited to, through-mask deposition,
integral shadow masking as described in US 5,276,380 and EP 0 732 868, laser
ablation, and selective chemical vapor deposition.

Hole-Injecting Layer (HIL)
        A hole-injecting layer **105** may be provided between anode **103** and

10   hole-transporting layer **107**. The hole-injecting material can serve to improve the
film formation property of subsequent organic layers and to facilitate injection of
holes into the hole-transporting layer. Suitable materials for use in the hole-
injecting layer include, but are not limited to, porphyrinic compounds as described
in US 4,720,432, plasma-deposited fluorocarbon polymers as described in US

15   6,208,075, and some aromatic amines, for example, m-MTDATA (4,4',4"-tris[(3-
methylphenyl)phenylamino]triphenylamine). Alternative hole-injecting materials
reportedly useful in organic EL devices are described in EP 0 891 121 A1 and EP
1 029 909 A1.

Hole-Transporting Layer (HTL)

20   The hole-transporting layer **107** of the organic EL device contains
at least one hole-transporting compound such as an aromatic tertiary amine, where
the latter is understood to be a compound containing at least one trivalent nitrogen
atom that is bonded only to carbon atoms, at least one of which is a member of an
aromatic ring. In one form the aromatic tertiary amine can be an arylamine, such

25   as a monoarylamine, diarylamine, triarylamine, or a polymeric arylamine.
Exemplary monomeric triarylamines are illustrated by Klupfel et al. US 3,180,730.
Other suitable triarylamines substituted with one or more vinyl radicals and/or
comprising at least one active hydrogen containing group are disclosed by
Brantley et al US 3,567,450 and US 3,658,520.

30

A more preferred class of aromatic tertiary amines are those which include at least two aromatic tertiary amine moieties as described in US 4,720,432 and US 5,061,569. Such compounds include those represented by structural formula (A).

$$A \qquad Q_1{\diagdown}_G{\diagup}Q_2$$

5

wherein Q_1 and Q_2 are independently selected aromatic tertiary amine moieties and G is a linking group such as an arylene, cycloalkylene, or alkylene group of a carbon to carbon bond. In one embodiment, at least one of Q_1 or Q_2 contains a polycyclic fused ring structure, e.g., a naphthalene. When G is an aryl group, it is

10   conveniently a phenylene, biphenylene, or naphthalene moiety.

A useful class of triarylamines satisfying structural formula (A) and containing two triarylamine moieties is represented by structural formula (B):

$$B \qquad R_1{-}\underset{\displaystyle R_4}{\overset{\displaystyle R_2}{C}}{-}R_3$$
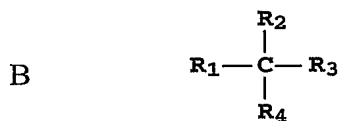
where

R_1 and R_2 each independently represents a hydrogen atom, an aryl group,

15   or an alkyl group or R_1 and R_2 together represent the atoms completing a cycloalkyl group; and

R_3 and R_4 each independently represents an aryl group, which is in turn substituted with a diaryl substituted amino group, as indicated by structural formula (C):

$$C \qquad \underset{\displaystyle R_6}{\overset{\displaystyle R_5}{N}}{-}$$

20   wherein R_5 and R_6 are independently selected aryl groups. In one embodiment, at least one of R_5 or R_6 contains a polycyclic fused ring structure, e.g., a naphthalene.

Another class of aromatic tertiary amines are the tetraaryldiamines. Desirable tetraaryldiamines include two diarylamino groups, such as indicated by

formula (C), linked through an arylene group. Useful tetraaryldiamines include
those represented by formula (D).

D R_7—N$\begin{smallmatrix}\\ Ar\end{smallmatrix}$—$\left(\!\!-Are\!\!-\right)_n$—N$\begin{smallmatrix}R_8\\ R_9\end{smallmatrix}$

wherein

each Are is an independently selected arylene group, such as a phenylene

5   or anthracene moiety,

n is an integer of from 1 to 4, and

Ar, R_7, R_8, and R_9 are independently selected aryl groups.

In a typical embodiment, at least one of Ar, R_7, R_8, and R_9 is a
polycyclic fused ring structure, e.g., a naphthalene

10   The various alkyl, alkylene, aryl, and arylene moieties of the
foregoing structural formulae (A), (B), (C), (D), can each in turn be substituted.
Typical substituents include alkyl groups, alkoxy groups, aryl groups, aryloxy
groups, and halogen such as fluoride, chloride, and bromide. The various alkyl and
alkylene moieties typically contain from about 1 to 6 carbon atoms. The cycloalkyl
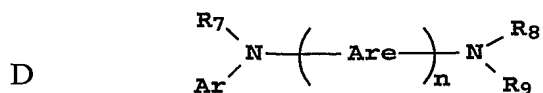
15   moieties can contain from 3 to about 10 carbon atoms, but typically contain five,
six, or seven ring carbon atoms--e.g., cyclopentyl, cyclohexyl, and cycloheptyl
ring structures. The aryl and arylene moieties are usually phenyl and phenylene
moieties.

The hole-transporting layer can be formed of a single or a mixture

20   of aromatic tertiary amine compounds. Specifically, one may employ a
triarylamine, such as a triarylamine satisfying the formula (B), in combination
with a tetraaryldiamine, such as indicated by formula (D). When a triarylamine is
employed in combination with a tetraaryldiamine, the latter is positioned as a layer
interposed between the triarylamine and the electron injecting and transporting

25   layer. Illustrative of useful aromatic tertiary amines are the following:

1,1-Bis(4-di-*p*-tolylaminophenyl)cyclohexane

1,1-Bis(4-di-*p*-tolylaminophenyl)-4-phenylcyclohexane

N,N,N',N'-tetraphenyl-4,4'''-diamino-1,1':4',1'':4'',1'''-quaterphenyl

Bis(4-dimethylamino-2-methylphenyl)phenylmethane

1,4-bis[2-[4-[N,N-di(p-toly)amino]phenyl]vinyl]benzene (BDTAPVB)

N,N,N',N'-Tetra-*p*-tolyl-4,4'-diaminobiphenyl

N,N,N',N'-Tetraphenyl-4,4'-diaminobiphenyl

N,N,N',N'-tetra-1-naphthyl-4,4'-diaminobiphenyl

5   N,N,N',N'-tetra-2-naphthyl-4,4'-diaminobiphenyl

N-Phenylcarbazole

4,4'-Bis[N-(1-naphthyl)-N-phenylamino]biphenyl (NPB)

4,4'-Bis[N-(1-naphthyl)-N-(2-naphthyl)amino]biphenyl (TNB)

4,4'-Bis[N-(1-naphthyl)-N-phenylamino]p-terphenyl

10   4,4'-Bis[N-(2-naphthyl)-N-phenylamino]biphenyl

4,4'-Bis[N-(3-acenaphthenyl)-N-phenylamino]biphenyl

1,5-Bis[N-(1-naphthyl)-N-phenylamino]naphthalene

4,4'-Bis[N-(9-anthryl)-N-phenylamino]biphenyl

4,4'-Bis[N-(1-anthryl)-N-phenylamino]-*p*-terphenyl

15   4,4'-Bis[N-(2-phenanthryl)-N-phenylamino]biphenyl

4,4'-Bis[N-(8-fluoranthenyl)-N-phenylamino]biphenyl

4,4'-Bis[N-(2-pyrenyl)-N-phenylamino]biphenyl

4,4'-Bis[N-(2-naphthacenyl)-N-phenylamino]biphenyl

4,4'-Bis[N-(2-perylenyl)-N-phenylamino]biphenyl

20   4,4'-Bis[N-(1-coronenyl)-N-phenylamino]biphenyl

2,6-Bis(di-*p*-tolylamino)naphthalene

2,6-Bis[di-(1-naphthyl)amino]naphthalene

2,6-Bis[N-(1-naphthyl)-N-(2-naphthyl)amino]naphthalene

N,N,N',N'-Tetra(2-naphthyl)-4,4''-diamino-*p*-terphenyl

25   4,4'-Bis{N-phenyl-N-[4-(1-naphthyl)-phenyl]amino}biphenyl

2,6-Bis[N,N-di(2-naphthyl)amino]fluorene

4,4',4''-tris[(3-methylphenyl)phenylamino]triphenylamine (MTDATA)

4,4'-Bis[N-(3-methylphenyl)-N-phenylamino]biphenyl (TPD)

Another class of useful hole-transporting materials includes

30   polycyclic aromatic compounds as described in EP 1 009 041. Tertiary aromatic

amines with more than two amine groups may be used including oligomeric

materials. In addition, polymeric hole-transporting materials can be used such as
poly(N-vinylcarbazole) (PVK), polythiophenes, polypyrrole, polyaniline, and
copolymers such as poly(3,4-ethylenedioxythiophene) / poly(4-styrenesulfonate)
also called PEDOT/PSS.

5   Fluorescent Light-Emitting Materials and Layers (LEL)

In addition to the phosphorescent materials of this invention, other
light emitting materials may be used in the OLED device, including fluorescent
materials. Although the term "fluorescent" is commonly used to describe any
light emitting material, in this case we are referring to a material that emits light

10   from a singlet excited state. Fluorescent materials may be used in the same layer as
the phosphorescent material, in adjacent layers, in adjacent pixels, or any
combination. Care must be taken not to select materials that will adversely affect
the performance of the phosphorescent materials of this invention. One skilled in
the art will understand that triplet excited state energies of materials in the same

15   layer as the phosphorescent material or in an adjacent layer must be appropriately
set so as to prevent unwanted quenching.

As more fully described in U.S. Patent Nos. 4,769,292 and
5,935,721, the light-emitting layer (LEL) of the organic EL element includes a
luminescent fluorescent or phosphorescent material where electroluminescence is

20   produced as a result of electron-hole pair recombination in this region. The light-
emitting layer can be comprised of a single material, but more commonly consists
of a host material doped with a guest emitting material or materials where light
emission comes primarily from the emitting materials and can be of any color. The
host materials in the light-emitting layer can be an electron-transporting material,

25   as defined below, a hole-transporting material, as defined above, or another
material or combination of materials that support hole-electron recombination. .
Fluorescent emitting materials are typically incorporated at 0.01 to 10 % by weight
of the host material.

The host and emitting materials can be small non-polymeric
30   molecules or polymeric materials such as polyfluorenes and polyvinylarylenes

(e.g., poly(p-phenylenevinylene), PPV).. In the case of polymers, small molecule emitting materials can be molecularly dispersed into a polymeric host, or the emitting materials can be added by copolymerizing a minor constituent into a host polymer. Host materials may be mixed together in order to improve film

5   formation, electrical properties, light emission efficiency, lifetime, or manufacturability. The host may comprise a material that has good hole-transporting properties and a material that has good electron-transporting properties.

An important relationship for choosing a fluorescent dye as a guest

10   emitting material is a comparison of the singlet excited state energies of the host and light-emitting material. For efficient energy transfer from the host to the emitting material, a highly desirable condition is that the singlet excited state energy of the emitting material is lower than that of the host material.

Host and emitting materials known to be of use include, but are not

15   limited to, those disclosed in US 4,768,292, US 5,141,671, US 5,150,006, US 5,151,629, US 5,405,709, US 5,484,922, US 5,593,788, US 5,645,948, US 5,683,823, US 5,755,999, US 5,928,802, US 5,935,720, US 5,935,721, and US 6,020,078.

Metal complexes of 8-hydroxyquinoline and similar derivatives

20   (Formula E) constitute one class of useful host compounds capable of supporting electroluminescence, and are particularly suitable for light emission of wavelengths longer than 500 nm, e.g., green, yellow, orange, and red.

E
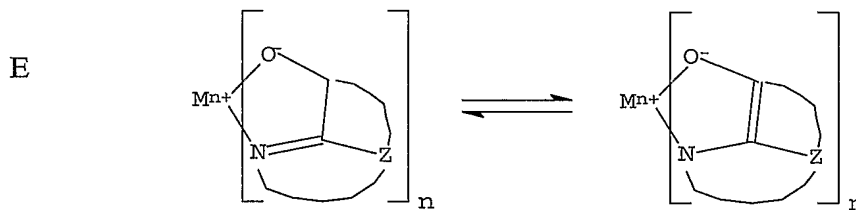
wherein

M represents a metal; n is an integer of from 1 to 4; and

25   Z independently in each occurrence represents the atoms completing a nucleus having at least two fused aromatic rings.

From the foregoing it is apparent that the metal can be monovalent, divalent, trivalent, or tetravalent metal. The metal can, for example, be an alkali metal, such as lithium, sodium, or potassium; an alkaline earth metal, such as magnesium or calcium; an earth metal, such aluminum or gallium, or a transition

5   metal such as zinc or zirconium. Generally any monovalent, divalent, trivalent, or tetravalent metal known to be a useful chelating metal can be employed.

Z completes a heterocyclic nucleus containing at least two fused aromatic rings, at least one of which is an azole or azine ring. Additional rings, including both aliphatic and aromatic rings, can be fused with the two required

10 rings, if required. To avoid adding molecular bulk without improving on function the number of ring atoms is usually maintained at 18 or less.

Illustrative of useful chelated oxinoid compounds are the following:

CO-1: Aluminum trisoxine [alias, tris(8-quinolinolato)aluminum(III)]

15 CO-2: Magnesium bisoxine [alias, bis(8-quinolinolato)magnesium(II)]

CO-3: Bis[benzo{f}-8-quinolinolato]zinc (II)

CO-4: Bis(2-methyl-8-quinolinolato)aluminum(III)-μ-oxo-bis(2-methyl-8-quinolinolato) aluminum(III)

CO-5: Indium trisoxine [alias, tris(8-quinolinolato)indium]

20 CO-6: Aluminum tris(5-methyloxine) [alias, tris(5-methyl-8-quinolinolato) aluminum(III)]

CO-7: Lithium oxine [alias, (8-quinolinolato)lithium(I)]

CO-8: Gallium oxine [alias, tris(8-quinolinolato)gallium(III)]

CO-9: Zirconium oxine [alias, tetra(8-quinolinolato)zirconium(IV)]

25 Derivatives of 9,10-di-(2-naphthyl)anthracene (Formula F) constitute one class of useful host materials capable of supporting electroluminescence, and are particularly suitable for light emission of wavelengths longer than 400 nm, e.g., blue, green, yellow, orange or red.

30

| F | |
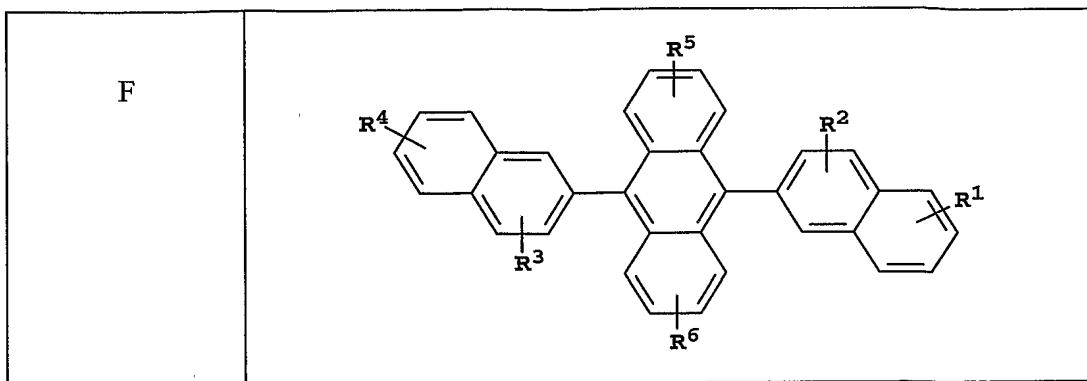
wherein: R^1, R^2, R^3, R^4, R^5, and R^6 represent one or more substituents on each ring where each substituent is individually selected from the following groups:

Group 1: hydrogen, or alkyl of from 1 to 24 carbon atoms;

Group 2: aryl or substituted aryl of from 5 to 20 carbon atoms;

Group 3: carbon atoms from 4 to 24 necessary to complete a fused aromatic ring of anthracenyl; pyrenyl, or perylenyl;

Group 4: heteroaryl or substituted heteroaryl of from 5 to 24 carbon atoms as necessary to complete a fused heteroaromatic ring of furyl, thienyl, pyridyl, quinolinyl or other heterocyclic systems;

Group 5: alkoxylamino, alkylamino, or arylamino of from 1 to 24 carbon atoms; and

Group 6: fluorine, chlorine, bromine or cyano.

Illustrative examples include 9,10-di-(2-naphthyl)anthracene and 2-*t*-butyl-9,10-di-(2-naphthyl)anthracene. Other anthracene derivatives can be useful as a host in the LEL, including derivatives of 9,10-bis[4-(2,2-diphenylethenyl)phenyl]anthracene.

Benzazole derivatives (Formula G) constitute another class of useful host materials capable of supporting electroluminescence, and are particularly suitable for light emission of wavelengths longer than 400 nm, e.g., blue, green, yellow, orange or red.
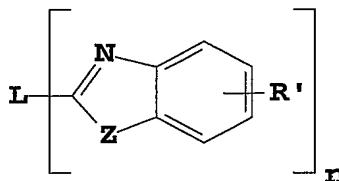
G

Where:

       n is an integer of 3 to 8;

       Z is O, NR or S; and
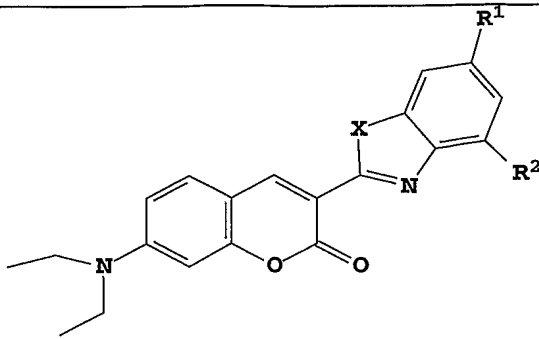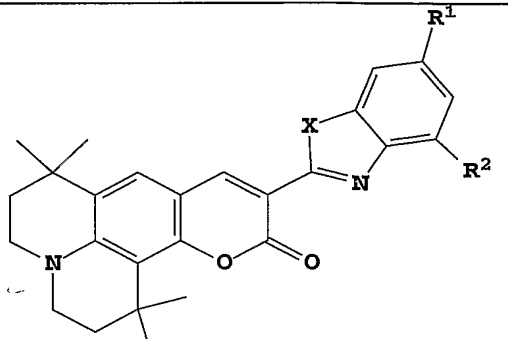
       R and R' are individually hydrogen; alkyl of from 1 to 24 carbon atoms, for example, propyl, t-butyl, heptyl, and the like; aryl or hetero-atom substituted aryl of from 5 to 20 carbon atoms for example phenyl and naphthyl, furyl, thienyl, pyridyl, quinolinyl and other heterocyclic systems; or halo such as chloro, fluoro; or atoms necessary to complete a fused aromatic ring; and
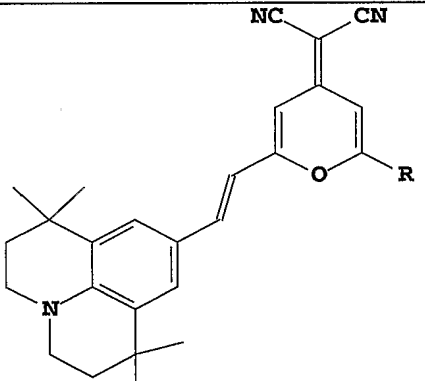
       L is a linkage unit consisting of alkyl, aryl, substituted alkyl, or substituted aryl, which conjugately or unconjugately connects the multiple benzazoles together. An example of a useful benzazole is 2, 2', 2''-(1,3,5-phenylene)tris[1-phenyl-1H-benzimidazole].
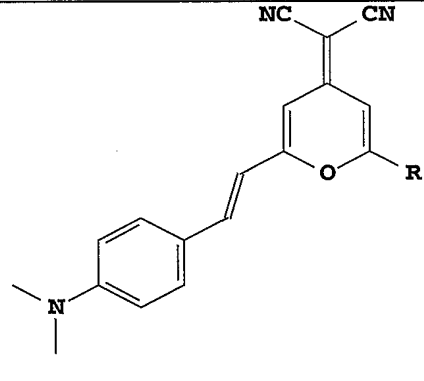
       Styrylarylene derivatives as described in U.S. Patent 5,121,029 and JP 08333569 are also useful hosts for blue emission. For example, 9,10-bis[4-(2,2-diphenylethenyl)phenyl]anthracene and 4,4'-Bis(2,2-diphenylethenyl)-1,1'-biphenyl (DPVBi) are useful hosts for blue emission.

       Useful fluorescent emitting materials include, but are not limited to, derivatives of anthracene, tetracene, xanthene, perylene, rubrene, coumarin, rhodamine, and quinacridone, dicyanomethylenepyran compounds, thiopyran compounds, polymethine compounds, pyrilium and thiapyrilium compounds, fluorene derivatives, periflanthene derivatives, indenoperylene derivatives, bis(azinyl)amine boron compounds, bis(azinyl)methane compounds, and carbostyryl compounds. Illustrative examples of useful materials include, but are not limited to, the following:

L1	L2
L3	L4
L5	L6
L7	L8

	X	R1	R2
L9	O	H	H
L10	O	H	Methyl
L11	O	Methyl	H
L12	O	Methyl	Methyl
L13	O	H	t-butyl
L14	O	t-butyl	H
L15	O	t-butyl	t-butyl
L16	S	H	H
L17	S	H	Methyl
L18	S	Methyl	H
L19	S	Methyl	Methyl
L20	S	H	t-butyl
L21	S	t-butyl	H
L22	S	t-butyl	t-butyl

	X	R1	R2
L23	O	H	H
L24	O	H	Methyl
L25	O	Methyl	H
L26	O	Methyl	Methyl
L27	O	H	t-butyl
L28	O	t-butyl	H
L29	O	t-butyl	t-butyl
L30	S	H	H
L31	S	H	Methyl
L32	S	Methyl	H
L33	S	Methyl	Methyl
L34	S	H	t-butyl
L35	S	t-butyl	H
L36	S	t-butyl	t-butyl

	R
L37	phenyl
L38	methyl
L39	t-butyl
L40	mesityl

	R
L41	phenyl
L42	methyl
L43	t-butyl
L44	mesityl

43

L45

L46

L47

L48

L49

L50

L51

L52
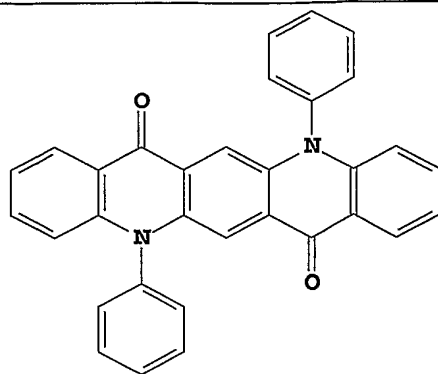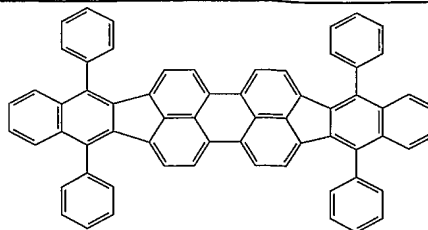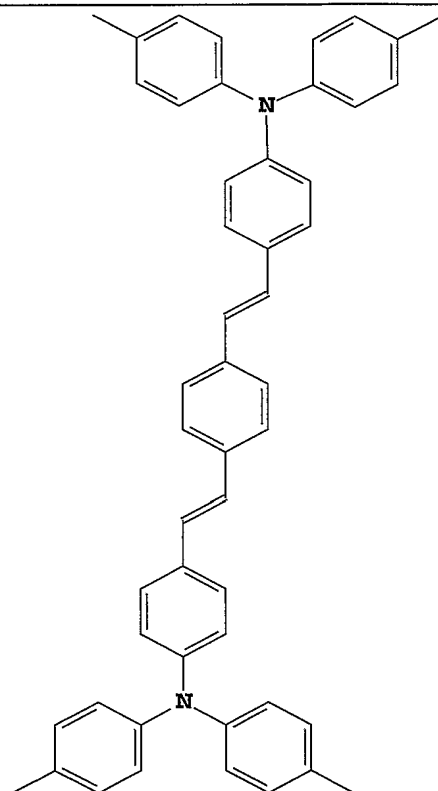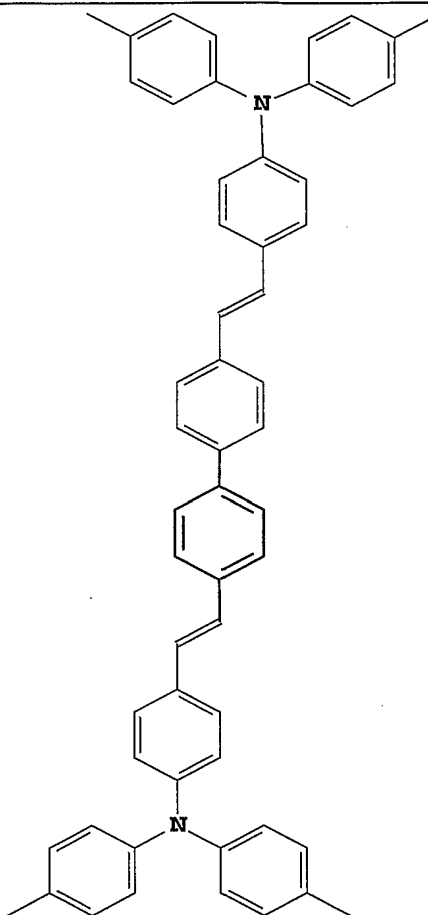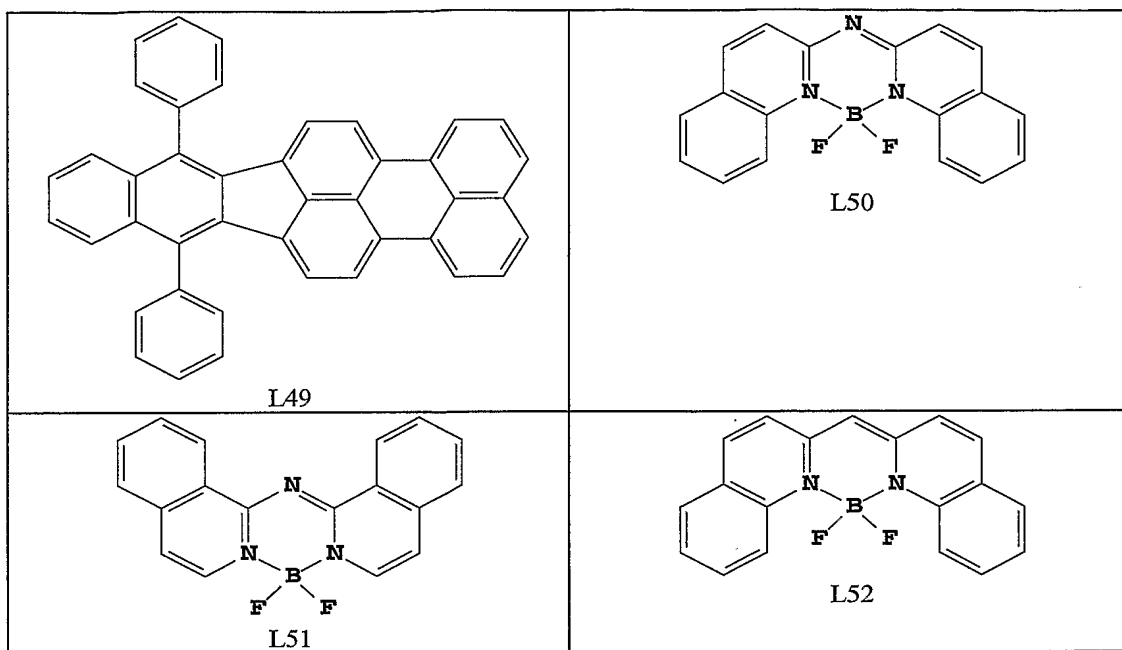
Electron-Transporting Layer (ETL)

Preferred thin film-forming materials for use in forming the electron-transporting layer **111** of the organic EL devices of this invention are metal chelated oxinoid compounds, including chelates of oxine itself (also commonly referred to as 8-quinolinol or 8-hydroxyquinoline). Such compounds help to inject and transport electrons and exhibit both high levels of performance and are readily fabricated in the form of thin films. Exemplary of contemplated oxinoid compounds are those satisfying structural formula (E),·previously described.

Other electron-transporting materials include various butadiene derivatives as disclosed in US 4,356,429 and various heterocyclic optical brighteners as described in US 4,539,507. Benzazoles satisfying structural formula (G) are also useful electron transporting materials. Triazines are also known to be useful as electron transporting materials.

Other Useful Organic Layers and Device Architecture

In some instances, layers **109** through **111** can optionally be collapsed into a single layer that serves the function of supporting both light

emission and electron transportation. Layers **110** and **111** may also be collapsed into a single layer that functions to block holes or excitons, and supports electron transportation. It also known in the art that emitting materials may be included in the hole-transporting layer, which may serve as a host. Multiple materials may be

5   added to one or more layers in order to create a white-emitting OLED, for example, by combining blue- and yellow-emitting materials, cyan- and red-emitting materials, or red-, green-, and blue-emitting materials. White-emitting devices are described, for example, in EP 1 187 235, US 20020025419, EP 1 182 244, US 5,683,823, US 5,503,910, US 5,405,709, and US 5,283,182 and can be

10   equipped with a suitable filter arrangement to produce a color emission.

          This invention may be used in so-called stacked device architecture, for example, as taught in US 5,703,436 and US 6,337,492.

Deposition of Organic Layers

          The organic materials mentioned above are suitably deposited by

15   any means suitable for the form of the organic materials. In the case of small molecules, they are conveniently deposited through sublimation, but can be deposited by other means such as from a solvent with an optional binder to improve film formation. If the material is a polymer, solvent deposition is usually preferred. The material to be deposited by sublimation can be vaporized from a

20   sublimator "boat" often comprised of a tantalum material, e.g., as described in US 6,237,529, or can be first coated onto a donor sheet and then sublimed in closer proximity to the substrate. Layers with a mixture of materials can utilize separate sublimator boats or the materials can be pre-mixed and coated from a single boat or donor sheet. Patterned deposition can be achieved using shadow masks, integral

25   shadow masks (US 5,294,870), spatially-defined thermal dye transfer from a donor sheet (US 5,688,551, US 5,851,709 and US 6,066,357) and inkjet method (US 6,066,357).

Encapsulation

          Most OLED devices are sensitive to moisture or oxygen, or both,

30   so they are commonly sealed in an inert atmosphere such as nitrogen or argon,

along with a desiccant such as alumina, bauxite, calcium sulfate, clays, silica gel,

zeolites, alkaline metal oxides, alkaline earth metal oxides, sulfates, or metal

halides and perchlorates. Methods for encapsulation and desiccation include, but

are not limited to, those described in U.S. Patent No. 6,226,890. In addition,

5   barrier layers such as SiOx, Teflon, and alternating inorganic/polymeric layers are

known in the art for encapsulation.

Optical Optimization

OLED devices of this invention can employ various well-known

optical effects in order to enhance its properties if desired. This includes

10   optimizing layer thicknesses to yield maximum light transmission, providing

dielectric mirror structures, replacing reflective electrodes with light-absorbing

electrodes, providing anti-glare or anti-reflection coatings over the display,

providing a polarizing medium over the display, or providing colored, neutral

density, or color-conversion filters over the display. Filters, polarizers, and anti-

15   glare or anti-reflection coatings may be specifically provided over the cover or as

part of the cover.

The invention and its advantages can be better appreciated by the

following examples.

20   Synthetic example 1

This example illustrates the preparation of the platinum complexes

of the invention. The tridentate ligand 1,3-di(2-pyridyl)benzene was prepared by

the following procedure. A solution of 2-bromopyridine (12.38 g, 78.4 mmol) in

anhydrous THF (100 mL) was cooled with a dry ice-acetone bath and was added

25   dropwise to a solution of n-BuLi in hexanes (53.6 mL, 1.6 M, 85.8 mmol) under

nitrogen atmosphere. After addition was complete (ca. 30 min), the resultant

mixture was stirred at −78 °C for 30 min. A solution of $ZnCl_2$ in Et_2O (50 mL, 1.0

M, 50 mmol, Aldrich) was added slowly into the reaction mixture via syringe (ca.

10 min). The dry ice-acetone bath was removed after the addition of $ZnCl_2$ and

30   the mixture was warmed to room temperature. $Pd(PPh_3)_4$ (1.84 g, 1.6 mmol,

Aldrich) was added to the reaction mixture and followed by 1,3-dibromobenzene

(6.14g, 26 mmol). The mixture was stirred at room temperature for 3 h then refluxed for 22 h. After cooling to room temperature, the mixture was quenched with MeOH (10 mL). The crude product was purified by repeated chromatography on silica gel with CH_2Cl_2-EtOAc (from 6:1 to 4:1). This afforded 4.78 g of 1,3-di(2-pyridyl)benzene, 79% yield; ^1H NMR Spectrum (300 MHz, $CDCl_3$, TMS): δ 7.1-7.2 (m, 2 H), 7.55 (t, J = 7.6 Hz, 1 H), 7.65-7.7 (m, 2 H), 7.75-8.1 (m, 2 H), 8.65-8.7 (m, 3 H); ^{13}C NMR spectrum(75 MHz, CDCl3, TMS): δ 120.42 (2C), 122.01 (2C), 125.25, 127.19 (2C), 128.96, 136.51 (2C), 139.59 (2C), 149.37 (2C), 156.84 (2C).

The complex Inv-1 was prepared according to the literature procedure by the reaction of potassium tetrachloroplatinate with 1,3-di(2-pyridyl)benzene in acetic acid at 110-115 °C for 3 days (D. Cardenas, A. Echavarren, M. Ramirez de Arellano, *Organometallic* , **18**, 3337 (1999)) and purified by flash chromatography on silica gel with CH_2Cl_2-EtOAc (9:1) eluent. A sublimed sample was used for OLED device preparation.

The emission spectra of Inv-1 was obtained at room temperature in ethyl acetate solution using a procedure well known to those skilled in the art (see, for example, C.A. Parker and W.T. Rees, *Analyst*, **85**, 587 (1960)). Compound Inv-1 had a λmax of emission of 488 nm with a quantum yield of 0.271.

Synthetic example 2

Synthesis of complex Inv-3

Inv-1   Inv-3
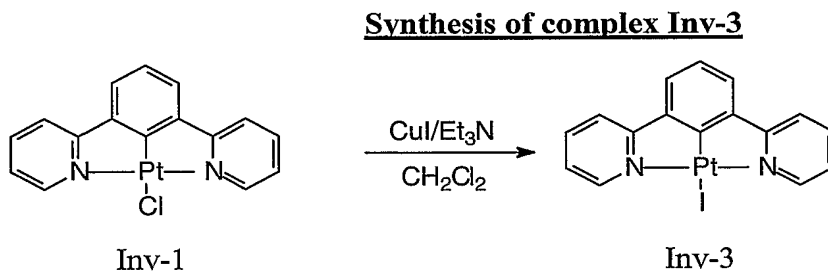
The complex Inv-3 was prepared as follows: A mixture of complex Inv-1 (0.46g, 1 mmol), CuI (0.57 g, 3 mmol), dichloromethane (100 mL), and triethylamine (10 mL) was stirred under nitrogen atmosphere at room temperature

until starting material complex Inv-1 disappeared as checked by TLC. The solvents were removed and the residue was dissolved in a minimum amount of dichloromethane and purified by flash chromatography on silica gel with dichloromethane as eluent. First yellow band was collected and evaporated to give the desired complex Inv-3 as a yellow crystalline material, 0.47 g, 85%. 0.35 g of this material was sublimed at 250-260 °C to provide 0.25 g of pure sample for device fabrication.

Synthetic example 3

Synthesis of complex Inv-101

Inv-101
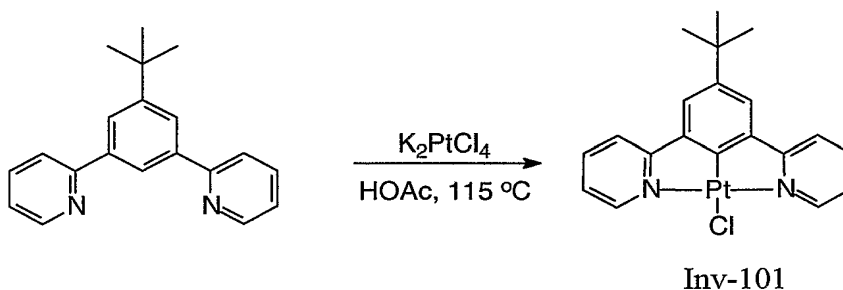
A mixture of 3,5-dipyridyl-1-tert-butylbenzene (1.27 g, 4.4 mmol), K$_2$PtCl$_4$ (1.8 g, 4.3 mmol), and acetic acid (120 mL) was degassed and stirred at 115-120 °C for 44 h. The reaction mixture was filtered while it was hot. The filtrate was cooled to room temperature and fine yellow brown needles were formed. The needles were collected by filtration, washed thoroughly with methanol, and dried overnight at 50 °C under reduced pressure to provide 1.48g of complex Inv-101. The filtrate was evaporated to dryness and the residue was purified by chromatography on silica gel with dichloromethane-ethyl acetate (v/v = 95/5) as eluent to provide additional 0.42 g of product Inv-101, total yield of 85%. 0.5 g of this material was sublimed at 250-255 °C to provide 0.42 g of pure sample for device fabrication.

Synthetic example 4

Synthesis of complex Inv-102:

Inv-102

This complex was prepared according to the procedure for the
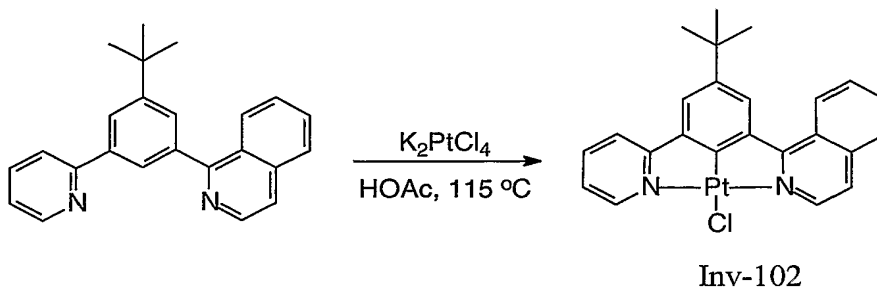
complex Inv-1. The crude product was purified by chromatography on silica gel

with dichloromethane and ethyl acetate (v/v = 9/1) as eluent. Sublimation of the

purified material provided red crystals for device fabrication. A single crystal was

selected for X-ray structure determination, which confirmed the proposed structure

for the complex Inv-102.

Device Example 1

An EL device (Sample 1) satisfying the requirements of the

invention was constructed in the following manner:

1.   A glass substrate coated with an 85 nm layer of indium-tin oxide

(ITO) as the anode was sequentially ultrasonicated in a commercial

detergent, rinsed in deionized water, degreased in toluene vapor and exposed

to oxygen plasma for about 1 min.

2.   Over the ITO was deposited a 1 nm fluorocarbon (CFx) hole-

injecting layer (HIL) by plasma-assisted deposition of CHF₃.

3.   A hole-transporting layer (HTL)of *N,N'*-di-1-naphthyl-*N,N'*-

diphenyl-4, 4'-diaminobiphenyl (NPB) having a thickness of 75 nm was then

evaporated from a tantalum boat.

4.   A 35 nm light-emitting layer (LEL) of 4,4'-N,N'-dicarbazole-

biphenyl (CBP) and Inv-1 (2 % wt%) were then deposited onto the hole-

transporting layer. These materials were also evaporated from tantalum

boats.

5.   A hole-blocking layer of bathocuproine (BCP) having a thickness

of 10 nm was then evaporated from a tantalum boat.

6.   A 40 nm electron-transporting layer (ETL) of tris(8-quinolinolato)aluminum (III) (AlQ₃) was then deposited onto the light-emitting layer. This material was also evaporated from a tantalum boat.

7.   On top of the AlQ₃ layer was deposited a 220 nm cathode formed of a 10:1 volume ratio of Mg and Ag.

The above sequence completed the deposition of the EL device. The device was then hermetically packaged in a dry glove box for protection against ambient environment.

Samples 2 and 3 were fabricated in an identical manner to Sample 1 except emitter Inv-1 was used at levels indicated in the table. Sample 4 was fabricated in an identical manner to Sample 1 except compound Inv-1 was not included. The cells thus formed were tested for luminance and color at an operating current of 20 mA/cm^2 and the results are reported in Table 1 in the form of luminance, emission wavelength and CIE (Commission Internationale de L'Eclairage) coordinates

Table 1. Evaluation Results for EL devices.

Sample	Inv-1 (%)	Luminance (cd/m^2)	Emission λmax	CIEx	CIEy	Type
1	2	3201	496	0.233	0.602	Invention
2	4	3511	496	0.238	0.606	Invention
3	6	3016	496	0.246	0.603	Invention
4	0	113	456	0.184	0.210	Comparison

As can be seen from Table 1, all tested EL devices incorporating the invention emitting material demonstrated a superior green color and higher luminance relative to the comparative device without the material.

Device Example 2 - Comparative

An EL device, Sample 5, was constructed and evaluated in the same manner as Sample 1 described above, except Com-1 was used in place of Inv-1. Samples 6 and 7 were prepared and evaluated in the same manner as Sample 5, except emitter Com-1 was used at the level indicated in Table 2.
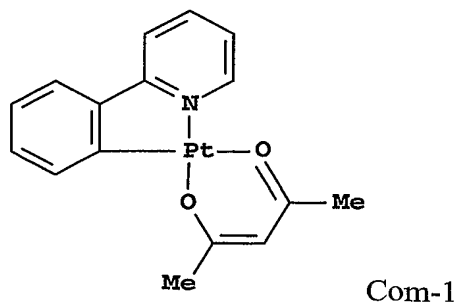
Com-1

Table 2. Evaluation Results for EL devices.

Sample	Com-1 Level (%)	Lumiance (cd/m²)	Efficiency (W/A)	CIEx	CIEy	Type
5	2	424	0.019	0.249	0.457	Comparison
6	4	595	0.025	0.296	0.489	Comparison
7	6	711	0.030	0.330	0.498	Comparison

As can be seen from Table 2, all tested EL devices incorporating the comparative phosphorescent organometallic material demonstrated poor efficiency.

Device Example 3

Samples 8-11 were fabricated in an identical manner to Sample 1 except Inv-3 was used as the emitter at different levels as indicated in Table 3. The cells thus formed were tested for luminance and color at an operating current of 20 mA/cm² and the results are reported in Table 3 in the form of luminance, emission wavelength and CIE (Commission Internationale de L'Eclairage) coordinates.

Table 3. Evaluation Results for EL devices (20 mA/cm²).

Sample	Inv-3 (%)	Luminance (cd/m²)	Emission λmax	CIEx	CIEy	Type
8	2	3614	496	0.221	0.608	Invention
9	4	4257	500	0.238	0.620	Invention
10	6	3671	500	0.236	0.615	Invention
11	0	155	464	0.175	0.221	Comparison

Device Example 4

　　　　An EL device (Sample 12) satisfying the requirements of the invention was constructed in the following manner:

　　　　1.　　A glass substrate coated with an 85 nm layer of indium-tin oxide (ITO) as the anode was sequentially ultrasonicated in a commercial detergent, rinsed in deionized water, degreased in toluene vapor and exposed to oxygen plasma for about 1 min.

　　　　2.　　Over the ITO was deposited a 1 nm fluorocarbon (CFx) hole-injecting layer (HIL) by plasma-assisted deposition of CHF_3.

　　　　3.　　A hole-transporting layer (HTL)of N,N'-di-1-naphthyl-N,N'-diphenyl-4, 4'-diaminobiphenyl (NPB) having a thickness of 75 nm was then evaporated from a tantalum boat.

　　　　4.　　A 35 nm light-emitting layer (LEL) of 4,4'-N,N'-dicarbazole-biphenyl (CBP) and Inv-101 (2%) were then deposited onto the hole-transporting layer. These materials were also evaporated from tantalum boats.

　　　　5.　　A hole-blocking layer of bis(2-methyl-quinolinolate)(4-phenylphenolate) (Al (Balq)) having a thickness of 10 nm was then evaporated from a tantalum boat.

　　　　6.　　A 40 nm electron-transporting layer (ETL) of tris(8-quinolinolato)aluminum (III) (AlQ_3) was then deposited onto the light-emitting layer. This material was also evaporated from a tantalum boat.

　　　　7.　　On top of the AlQ_3 layer was deposited a 220 nm cathode formed of a 10:1 volume ratio of Mg and Ag.

　　　　The above sequence completed the deposition of the EL device. The device was then hermetically packaged in a dry glove box for protection against ambient environment.

　　　　Samples 13-15 were fabricated in an identical manner to Sample 12 except emitter Inv-101 was used at levels indicated in the table. The cells thus formed were tested for luminance and color at an operating current of 20 mA/cm^2

and the results are reported in Table 4 in the form of luminance, emission wavelength and CIE (Commission Internationale de L'Eclairage) coordinates.

Table 4. Evaluation Results for EL devices.

Sample	Inv-101 (%)	Luminance (cd/m^2)	Emission λmax	CIEx	CIEy	Type
12	2	2882	508	0.269	0.614	Invention
13	4	3665	508	0.276	0.627	Invention
14	6	3929	508	0.280	0.629	Invention
15	8	4033	508	0.286	0.627	Invention

Device Example 6

Samples 16-18 were fabricated in an identical manner to Sample 12 except Inv-102 was used as emitter at levels indicated in the table. The cells thus formed were tested for luminance and color at an operating current of 20 mA/cm^2 and the results are reported in Table 5 in the form of luminance, emission wavelength and CIE (Commission Internationale de L'Eclairage) coordinates.

Table 5. Evaluation Results for EL devices.

Sample	Inv-102 (%)	Luminance (cd/m^2)	Emission λmax	CIEx	CIEy	Type
16	6	453	604	0.585	0.385	Invention
17	8	524	604	0.596	0.382	Invention
18	10	444	604	0.613	0.368	Invention

The invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be affected within the scope of the invention. The entire contents of the patents and other publications referred to in this specification are incorporated herein by reference.

PARTS LIST

101	Substrate
103	Anode
105	Hole-Injecting layer (HIL)
107	Hole-Transporting layer (HTL)
109	Light-Emitting layer (LEL)
110	Hole-blocking layer (HBL)
111	Electron-Transporting layer (ETL)
113	Cathode

CLAIMS:

1.   An electroluminescent device comprising a light-emitting layer containing a light emitting material that contains an organometallic complex comprising a metal selected from the group consisting of Pt, Pd and Ir, and a tridentate (N^C^N) ligand, wherein the tridentate (N^C^N) ligand represents a ligand that coordinates to the metal through a nitrogen donor bond, a carbon-metal bond, and a nitrogen donor bond, in that order, wherein at least one of the nitrogen donors is part of an aromatic ring or an imine group.

2.   The device of Claim 1 wherein the metal is Pt.

3.   The device of Claim 1 wherein the organometallic complex is part of a compound containing two or more complexes.

4.   The device of Claim 1 wherein each of the nitrogen donors is part of an aromatic ring.

5.   The device of Claim 1 wherein the organometallic complex can be represented by Formula (1a),

(1a)
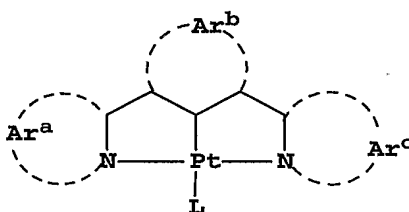
wherein:

        Ar^a, Ar^b, and Ar^c independently represent the atoms necessary to form a five or six-membered aromatic ring group; and

                L is an anionic ligand.

6.   The device of claim 5 wherein Ar^a, Ar^b, and Ar^c independently represent the atoms necessary to form a six-membered aromatic ring group.

7.   The device of claim 5 wherein Ar^a and Ar^c independently represent the atoms necessary to form a pyridine ring group.

8.   The device of claim 5 wherein Ar^b represents the atoms necessary to form a benzene ring group.

9.   The device of claim 5 wherein L represents halogen.

10.   The device of claim 5 wherein L represents a substituent that forms a carbon-platinum bond.

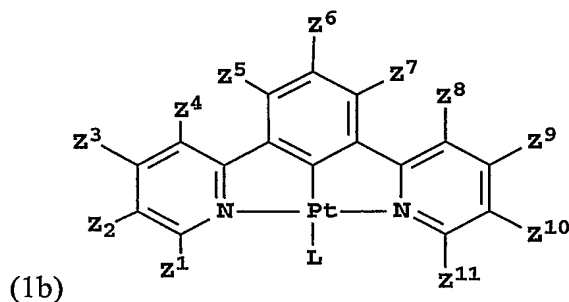11.   The device of claim 5 wherein L represents an alkynyl group, an alkenyl group, an aryl group, or an alkyl group.

12.   The device of claim 5 wherein L represents RX, wherein X represents a substituent that forms a bond to platinum and wherein X represents N, O, S, or Se, and R represents a substituent.

13.   The device of Claim 1 wherein the organometallic complex is represented by Formula (1b),
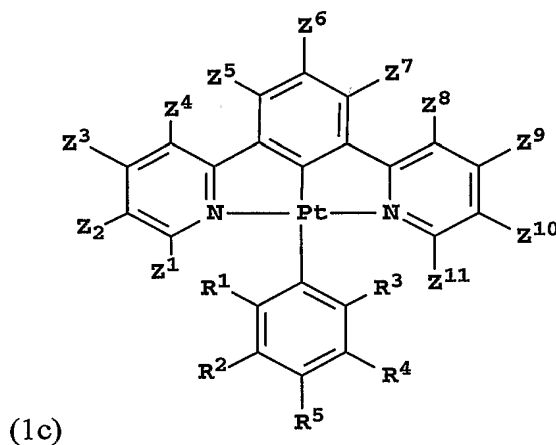

(1b)

wherein,

$Z^1 - Z^{11}$ represent hydrogen or independently selected substituent groups, provided that adjacent substituent groups can combine to form rings, and provided that Z^4 and Z^5, and Z^7 and Z^8 can also combine to form rings; and

L represents an anionic ligand.

14.   The device of claim 13 wherein L represents halogen, an alkynyl group, an alkenyl group, an aryl group, an alkyl group, or RX, wherein X represents a substituent that forms a bond to platinum and wherein X represents N, O, S, or Se, and R represents an aryl group, an alkyl group, a carbonyl group or a sulfonyl group.

15.   The device of Claim 1 wherein the organometallic complex can be represented by Formula (1c),

(1c)

wherein,

$Z^1 - Z^{11}$ represent independently selected substituent groups, provided that adjacent substituent groups can combine to form rings, and provided that Z^4 and Z^5, and Z^7 and Z^8 can also combine to form rings; and

$R^1 - R^5$ represent hydrogen or independently selected substituents, provided that adjacent substituent groups can combine to form rings.

16.   The device of claim 15 wherein R^1 and R^2 of Formula (1c) combine to form a six-membered ring group.

17.   The device of claim 15, wherein R^1 of Formula (1c) is a 1-12 carbon alkyl group.

18.   The device of claim 13, wherein R^1 and R^2, of Formula (1c), combine to form a six-membered ring group.

19.   The device of claim 13, wherein R^3 and R^4 also combine to form a six-membered ring group.

20.   The device of claim 13, wherein R^1 and R^3 independently represent a 1-12 carbon alkyl group.

21.   The device of claim 1 wherein the light-emitting material is disposed in a host material.

22.   The device of claim 21 wherein the light emitting material is present in an amount of up to 50 wt% based on the host.

23.   The device of claim 21 wherein the light emitting material is present in an amount of up to 15 wt% based on the host.

24.   The device of claim 1 capable of emitting white light.

25.   The device of claim 24 including a filtering means.

26.   The device of claim 1 including a fluorescent white light emitting material.

27.   The device of claim 1 wherein the organometallic complex contains a quinolinyl or isoquinolinyl group.

28.   A display comprising the OLED device of claim 1.

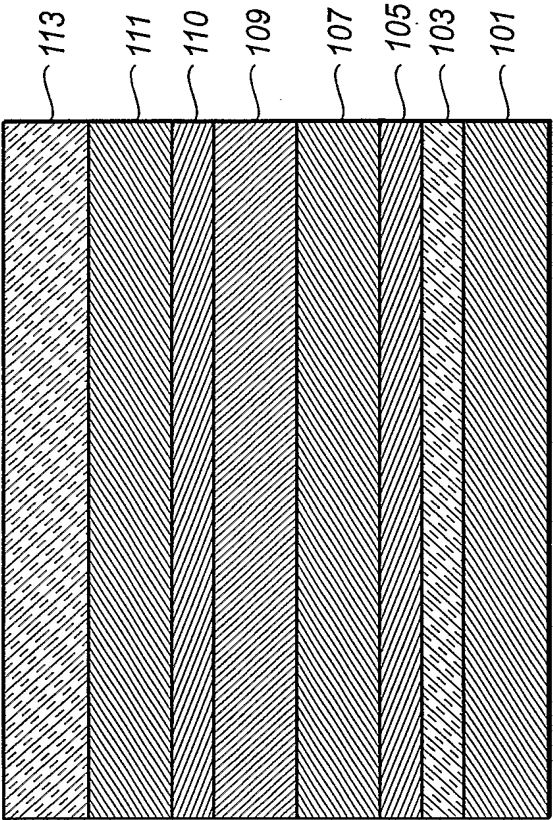29.   An area lighting device comprising the OLED device of
5   claim 1.

FIG. 1

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7   C09K11/06   H05B33/14   H01L51/20   H01L51/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7   C09K   H05B   H01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category°	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/039781 A (TAKASAGO INTERNATIONAL CORPORATION; ITOH, HISANORI; NAKAYAMA, YUJI; MA) 13 May 2004 (2004-05-13) * compounds at page 23 * abstract	1-29
X	US 2002/179885 A1 (CHE CHI-MING ET AL) 5 December 2002 (2002-12-05) * pages 2-4, Table I, Examples, claims *	1-29
A	WO 03/093283 A (THE UNIVERSITY OF HONG KONG) 13 November 2003 (2003-11-13) the whole document	1-29
A	WO 03/040257 A (E. I. DU PONT DE NEMOURS AND COMPANY; LECLOUX, DANIEL, DAVID; PETROV,) 15 May 2003 (2003-05-15) the whole document	1-29

☐ Further documents are listed in the continuation of box C.   ☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2005	24/03/2005

Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Nemes, C

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